# A Clinicopathological study of adult renal cell carcinoma with comparison and re-grading of Fuhrman system with ISUP 2012 – A 3 year retrospective study

**A DISSERTATION SUBMITTED IN PART FULFILMENT OF THE REGULATION**

**FOR THE AWARD OF THE DEGREE OF M.D. PATHOLOGY BRANCH III.**


THE TAMIL NADU DR. M.G.R. UNIVERSITY, CHENNAI, TAMILNADU

MAY-2019

# A Clinicopathological study of adult renal cell carcinoma with comparison and re-grading of Fuhrman system with ISUP 2012 – A 3 year retrospective study

**A dissertation in part fulfillment of the rules and regulations for the M.D. Branch III (Pathology) Degree Examination of the Tamil Nadu Dr. M.G.R Medical University, to be held in May 2019**

# CERTIFICATE

This is to certify that this dissertation titled **"A Clinicopathological study of adult renal cell carcinoma with comparison and re-grading of Fuhrman system with ISUP 2012 – A 3 year retrospective study"** is a bonafid work done in the department of general pathology by Dr. Santhosh Raj (Postgraduate Registrar), in part fulfillment of the rules and regulations for the M.D. Branch III (Pathology) Degree Examination of the Tamil Nadu Dr. M.G.R Medical University, to be held in May 2019.

Dr. Vivi M. Srivastava, MBBS, MD

Professor and Head,

Department of General Pathology,

Christian Medical College, Vellore.

Dr. Anna Pulimood, MBBS, MD

Principal,

Christian Medical College,

Vellore

# CERTIFICATE

This is to certify that this dissertation titled **"A Clinicopathological study of adult renal cell carcinoma with comparison and re-grading of Fuhrman system with ISUP 2012 – A 3 year retrospective study"** is a bonafide work done under my supervision by Dr. Santhosh Raj, in part fulfillment of the rules and regulations for the M.D. Branch III (Pathology) Degree Examination of the Tamil Nadu Dr. M.G.R Medical University, to be held in May 2019. The candidate has independently reviewed the literature, performed the data collection, analyzed the methodology and carried out the evaluation towards completion of the thesis.

Dr. Ramani Manoj Kumar

Associate Professor,

Department of General Pathology

Christian Medical College,

Vellore.

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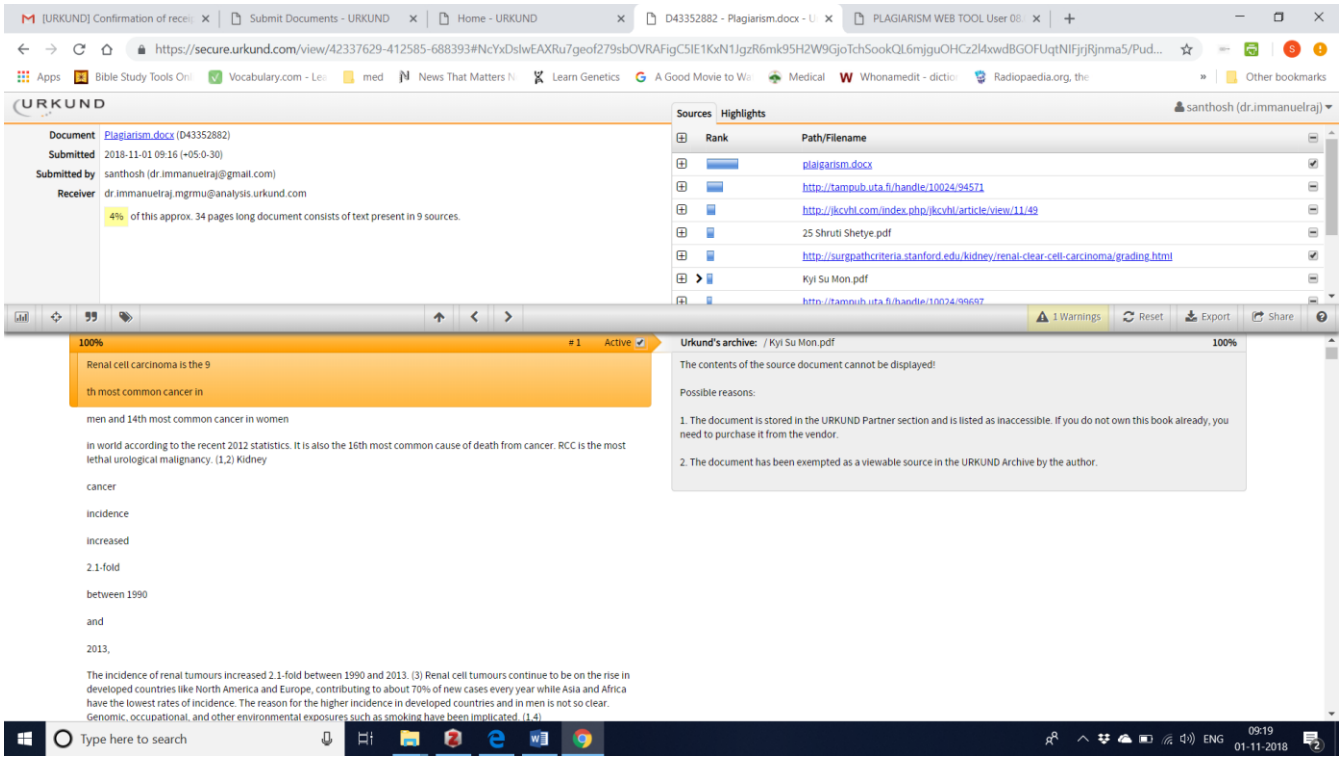
Dr. Santhosh Raj A,

Postgraduate Registrar,

Department of General Pathology

Christian Medical College, Vellore.

# ANTI-PLAGIARISM CERTIFICATE



This is to certify that this is the dissertation work entitled “A Clinicopathological study of adult renal cell carcinoma with comparison and re-grading of Fuhrman system with ISUP 2012 – A 3 year retrospective study” of the candidate Santhosh Raj with registration Number 201613356 for the award of Degree of MD Pathology in the Branch III. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows four percent (4%) of plagiarism in the dissertation.

Guide & Supervisor sign with Seal.

# ACKNOWLEDGEMENT

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At the end I thank God the almighty for giving me an opportunity to do my destined work.

- **Dr. SANTHOSH RAJ A**

# ABBREVATIONS

| | |
|---|---|
| **RCC** | Renal Cell Carcinoma |
| **ccRCC** | Clear cell renal cell carcinoma |
| **pRCC** | Papillary renal cell carcinoma |
| **ChRCC** | Chromophobe renal cell carcinoma |
| **sRCC** | Sarcomatoid renal cell carcinoma |
| **EMT** | Epithelial–mesenchymal transition |
| **VHL** | Von Hippel–Lindau |
| **ISUP** | International Society of Urological Pathology |
| **WHO** | World Health Organisation |

# Contents

# INTRODUCTION

Renal cell carcinoma is the 9th most common cancer in men and 14th most common cancer in women in world according to the recent 2012 statistics. It is also the 16th most common cause of death from cancer. RCC is the most lethal urological malignancy.(1,2)

The incidence of renal tumours increased 2.1-fold between 1990 and 2013.(3)

Renal cell tumours continue to be on the rise in developed countries like North America and Europe, contributing to about 70% of new cases every year while Asia and Africa have the lowest rates of incidence. The reason for the higher incidence in developed countries and in men is not so clear. Genomic, occupational, and other environmental exposures such as smoking have been implicated. (1,4)

Mortality is decreasing in the developed economies, but not so in case of low- and middle-income countries, where access to and the availability of optimal therapies are limited.(5)

# AIMS AND OBJECTIVES

i) Comparison of Fuhrman system of nuclear grading of renal cell carcinoma with ISUP 2012 grading and regrading where applicable.

ii) To study the microscopic features of clear cell and papillary renal cell carcinoma in adults.

iii) To determine event free survival in comparative grades.

# REVIEW OF LITERATURE

Historical perspective:

The earliest reference in literature about a tumour arising from the kidney was made by Daniel Sennert, a renowned German physician in his book “Practicae Medicinae” published in 1613, where under the term “Scirrhus renum” he explained as following. “Moreover the hard swelling of bad kidneys which has the capacity to throw a person into cachexia and dropsy, is for the greater part incurable”. (6)

The earliest confirmed case of renal tumour was in 1810 by Miriel and in 1826 followed by the first classification of renal tumors as proposed by Konig, which was based on the gross morphologic appearances into fungoid, medullary, scirrhous and steatomatous types.

Rayer, between 1831 and 1838 did a case series on renal tumours which was later published in the third volume of his “Treatise on Renal Disease” in 1841 where he had divided his cases on the basis of tumor morphology and clinical features into three categories namely: Latent cancer (encephaloid tumors without renal enlargement or hematuria), calyceal cancer (associated with renal pain and hematuria), and scirrhous carcinoma (often with hematuria).

After the publication of Rayer’s treatise, the focus got shifted back to histologic studies so as to determine the tissue of origin of the tumors and it was Robin in 1855 who described that the proliferating cells from the renal tubule epithelium formed nodules of tumor.

Virchow, described a subgroup of small, yellow, renal cortical tumours considered as lipomas apart from the tumours that arose from renal tubule as heteroplastic tumors.

Grawitz, in his 1883 study initially had described them as lipomas of the kidney. Following his second study he came to a conclusion that these tumors were derived from intrarenal adrenal rests.

Oberling et al settled the matter once for all regarding the origin of renal carcinoma through ultrastructural studies and concluded that they were derived from renal tubular epithelium. (7,8)

The first use of the term conventional RCC was used in 1997 classification of renal neoplasm to denote the clear cell variant(6).

## Global burden:

The global incidence of renal carcinomas increased 2.1-fold between 1990 and 2013. In the same period, deaths from it also increased across all sexes and age groups, with an annual rate of increase of 1.1%. The significance in developing countries is that though only 34.1% of the total new renal cancer diagnoses was being made in developing countries, yet they contributed to 41.6% of all deaths due to RCC which reflected on a poor survival.

By 2013, older individuals comprised the predominant population with up to 65% of RCC occurring in individuals aged 60 years and older when compared with 59.6% in 1990. Accordingly, there was also more mortality which occurred in those aged 60

years and older, from 65.1% in 1990 to 72.1% in 2013.(3)

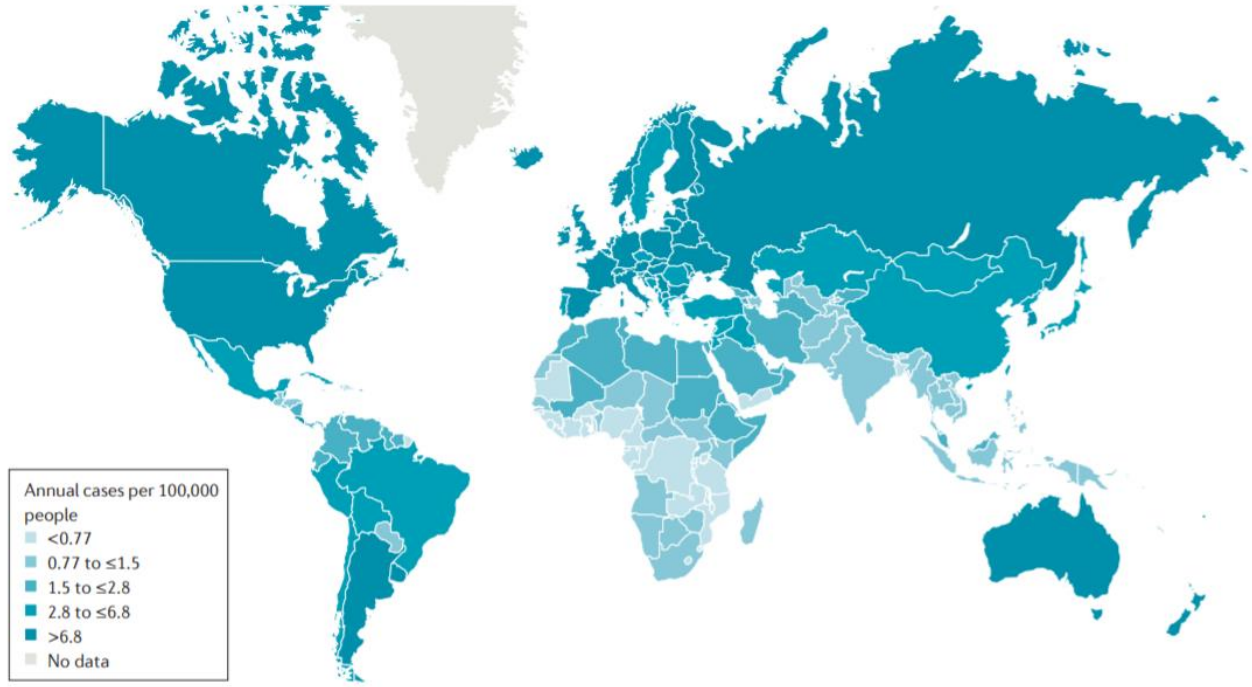



*Figure 1 Global Burden(9)*

## Risk factors:

The incidence of renal cell carcinoma markedly increases with age and is more common among males. The proven risk factors include obesity, hypertension and cigarette smoking. Other proven associated medical conditions are chronic kidney disease, hemodialysis, renal transplantation and acquired cystic kidney diseases.

Data linking physical activity to renal cell cancer risk is still limited, but most studies that examined have reported an inverse association.

### Cigarette Smoking

Cigarette smoking is considered a causal risk factor for renal cell cancer although the risk associated is relatively modest. A clear dose-response pattern of risk was

observed. Smoking cessation only among the long-term quitters of ten or more years reduces the risk.

Cigarette smoking is hypothesized to increase renal cell cancer risk through chronic tissue hypoxia due to carbon monoxide exposure and smoking-related conditions like chronic obstructive pulmonary disease. Deletions in chromosome 3p, a frequent site of genetic alterations in renal cell cancer, were commonly seen in cultured peripheral blood lymphocyte cells from renal cell cancer patients treated with benzo pyrene diol epoxide, a major constituent of cigarette smoke than control subjects.

Studies have also proven that in clear cell RCC the patients who were still smoking cigarettes at time of nephrectomy are at greater risk of death from RCC compared with non smokers. This relationship was explained by the observation that cigarette smokers are more likely to present with more advanced disease at time of surgery. This is possible either because smokers delay their diagnosis of ccRCC or smoking itself might affect ccRCC tumor biology and phenotype leading to development of tumors that invade and metastasize more readily. (10)

Obesity:

In prospective studies conducted worldwide, overweight and obese individuals were found to have elevated subsequent risks of renal cell cancer, with an estimated 24% increase for men and 34% for women for every 5 kg/m2 increase in body mass index.

The global rise in obesity possibly has also led to the upward RCC incidence trends. Several mechanisms have been hypothesized to influence renal cell cancer development in obese individuals, but direct evidence is limited. The mechanisms postulated include chronic tissue hypoxia, insulin resistance and a compensatory

hyperinsulinemia, altered endocrine milieu and production of adipokines, obesity-induced inflammatory response, lipid peroxidation and oxidative stress. (1)

Compared with stable weight, neither steady gain in weight nor weight loss was significantly associated with risk of RCC.(9)

Overweight and obesity are proven etiologies for RCC. Paradoxically, it was also observed that patients with a higher BMI had a significantly better prognosis than those with lower BMI. It is also proven that patients with a higher BMI were associated with lower grade of RCC in clinically localized renal masses .(11)

Tumors of obese patients may be more indolent than those of normal weight patients, a pattern that is also supported by the alterations in gene expression signatures.(12)

## Hypertension:

Though some renal tumors themselves can lead to hypertension there is enough evidence to demonstrate that hypertension predisposes to renal cell cancer development. Despite the high correlation between obesity and hypertension, their associations with renal cell cancer risk are independent of each other. Risk is higher among individuals who are both obese and hypertensive than those who have only one of these conditions.

The biologic mechanisms underlying the association between hypertension and renal cell cancer are unclear, but are hypothesized to include chronic renal hypoxia and lipid peroxidation with formation of reactive oxygen species. (13)

## Acquired cystic kidney disease:

Patients with end stage renal disease on haemodialysis have an increased propensity (3-7%) to develop renal cell carcinoma. These patients usually develop papillary renal cell carcinoma. However currently renal cancer associated with acquired cystic kidney disease is regarded as a separate entity on its own.

## Occupational exposure

There is a significant overall 1.3 relative risk of renal cancer associated with a chemical additive, Tricholoroethylene. There is no proven role for alcohol as a risk for renal cancer. In Caucasians and African Americans there is a relatively increased risk of developing RCC in the agricultural and dry-cleaning industries and especially for the ccRCC subtype.(1,14)

## Genetic susceptibility

Up to 4% of the renal carcinomas have a familial cause though most of them are sporadic. There is approximately double risk of renal cancer occurring in a first degree relative of the patient. Also each common histological type has its own familial cancer syndrome. (1)

## Pathogenesis:

Papillary and ccRCC appear to arise from the proximal tubule, while oncocytoma and chromophobe tumors arise from the distal tubule. Collecting duct and medullary RCC arise from the collecting ducts of Bellini and renal medulla, respectively.(15)

Chromosome 3p deletion is the most characteristic genetic abnormality found in sporadic clear cell renal cell carcinoma and it is regarded as an important step in tumor initiation. Different genes located on the short arm of chromosome 3 are probably involved in renal carcinoma but the most important of them is the von Hippel–Lindau disease tumor suppressor gene in 3p25-26. Other putative genes at 3p are PBRM and NRC-1

Papillary renal cell carcinoma shows characteristically trisomy/polysomy of chromosomes 3q, 7, 8, 12, 16, 17 and 20 and loss of the Y-chromosome. Hereditary papillary renal cell carcinoma is characterized by *c-met* proto-oncogene mutation on chromosome 7 but it is rare in sporadic papillary renal cell carcinoma.(16)

The VHL tumor suppressor gene, 3p25-26 gene as identified by positional cloning is altered in families with the von Hippel–Lindau familial cancer syndrome. ccRCC is one of those rare solid neoplasms in which almost all cases show a biallelic alteration of a single common tumor suppressor gene. Both familial and sporadic ccRCC clearly indicate that genetic alterations causing the loss of function of VHL must play a central pathogenic role in the evolution of this tumor type.

pVHL, the protein encoded by the VHL gene functions as an adaptor protein and helps in recruiting different effector proteins to different target proteins. Hence it regulates numerous different biochemical activities thereby controlling a variety of

cellular processes. Few of those cellular processes include targeting the hypoxia-inducible factor α (HIF-α) transcription factors for oxygen-dependent ubiquitin

mediated proteolytic degradation, regulating microtubule stability, activating p53, controlling neuronal apoptosis, suppressing epithelial to mesenchymal transition (EMT)/ cellular senescence and aneuploidy. Despite this several studies have illustrated that the transformation of normal kidney cells to ccRCC requires more than just the loss of VHL function.

Biallelic inactivation of pVHL function leads on to the constitutive stabilization of HIF-1α and HIF-2α, which in turn induces the expression of many overlapping and distinct, transcriptional targets.(17)

However recent large scale sequencing studies have led to identification of driver genes in ccRCC beyond VHL. These studies identified frequently mutated tumor suppressors, including PBRM1, BAP1 and SETD2, all of which function as chromatin and/or histone modifiers and also interestingly map to the frequently lost 3p21 locus. There is also suggestion that additional pathogenic mechanisms are at play and corroborate the suspicion that ccRCC is a metabolic disease, thereby potentially yielding novel therapeutic insights for renal carcinoma.(18)

## Epigenetic modifiers:

RCC is a heterogeneous disease which includes many different histological subtypes; of which clear cell renal cell carcinoma (ccRCC) is the commonest comprising up to 75% of RCCs, while papillary RCC (pRCC), chromophobe renal cell carcinoma (chRCC) and other rare tumour types, complete the remaining 25%.

There have been major therapeutic advances in the treatment of metastatic RCC over the past two decades, owing to the discovery of antiangiogenic targeted therapies and

immunotherapies. Despite these advances only a fraction of patients show durable clinical responses and long-term remission.

Chromatin modifiers play a role in regulating genomic architecture and hence control DNA accessibility. Chromatin modifiers also have non-histone substrates which participate in extranuclear processes like cytoskeletal dynamics and immune responses. Therefore loss-of-function mutations in chromatin modifiers, which are common in renal cell carcinoma (RCC), can modify tumour biology and influence therapeutic responses.

With the help of high-throughput sequencing efforts, mutations in a number of chromatin modifier genes have been identified which include PBRM1, SETD2, BAP1, KDM5C, KDM6A, and MLL2.

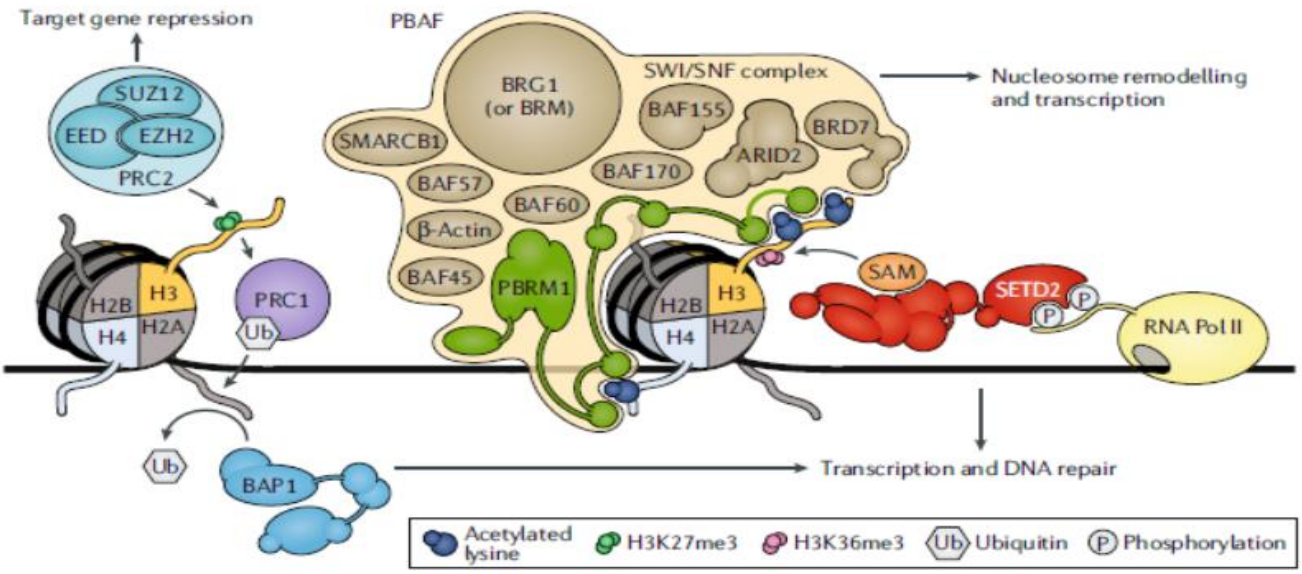



*Figure 2. Genes for histone modifying enzymes in ccRCC(19)*

In 2010, the targeted sequencing of 3,544 protein coding genes in 101 ccRCC samples unmasked mutations in four genes which encoded for histone modifying enzymes. These were histone-lysine N-methyltransferase SETD2, a histone H3 lysine 36

methyltransferase; lysine-specific demethylase 5C (KDM5C), a histone H3 lysine 4 demethylase; histone lysine N-methyltransferase 2D (KMT2D), a histone H3 lysine 4 methyltransferase; and lysine-specific demethylase 6A (KDM6A), a histone H3 lysine 27 demethylase17.

Other mutations were discovered in the genes that encoded for protein polybromo 1 (PBRM1), ubiquitin carboxyl-terminal hydrolase BAP1 (BAP1), AT-rich interactive domain-containing protein 1A (ARID1A), and ARID1B (ARID1B) were identified in ccRCC.

BAP1 is a deubiquitinase which targets mono ubiquitylation of lysine 119 on histone H2A, while PBRM1, ARID1A, and ARID1B are components of the switch/ sucrose non fermentable (SWI/SNF) chromatin re-modelling complex, which is involved in nucleosome repositioning. These enzymes have a common feature in that they participate in modifying chromatin structure. (19)

## Genetics of Sarcomatoid RCC

Sarcomatoid RCC exhibits a very aggressive behavior irrespective of the parent subtype with which it shares its histologic characteristics and constitutes up to 20% of stage IV RCC cases. The importance of this entity is that there are no established therapies which are effective.

Genome-wide analysis has shown that sRCC clusters according to parent subtype.

One another interesting observation is the fact that the sRCC—are prone not to show LOH at 3p21-25 and more importantly they retain a copy of the wild-type VHL and

PBRM1 genes. So it is not true that all ccRCC tumors show a 3p LOH/deletion event. Rather, it shows that sRCC tumor clones have a distinct early molecular pathogenesis. So though sRCC and ccRCC may originate from a common precursor, the molecular events are different, and sRCC does not evolve linearly from low-grade ccRCC. The significance is that if the diagnostic molecular assay fails to demonstrate a 3p or VHL deletion in a suspected ccRCC case it does not necessarily rule out a clear-cell subtype of RCC, particularly when associated with higher grade or sarcomatoid features.

Whereas mutations in 3p genes were confined to the ccRCC subtype, sRCC of other subtypes displayed mutations in PTEN, TP53, NF2, and RELN. Although mutations in these genes occurred in all sRCC subtypes, their specific association with sarcomatoid changes within a given subtype varied according to the gene.

To know if a patient with advanced disease has sarcomatoid features is relevant due to the frequent explosive growth of sarcomatoid tumors that dissuades clinicians from offering cytoreductive nephrectomy prior to initiating systemic therapy.

Despite all the advancements the ability to predict sRCC is not feasible at present, as there is no specific radiologic criteria or tissue biomarkers. Moreover, biopsy prediction of RCC tumor grade is notoriously unreliable, including predicting for sarcomatoid change.(20)

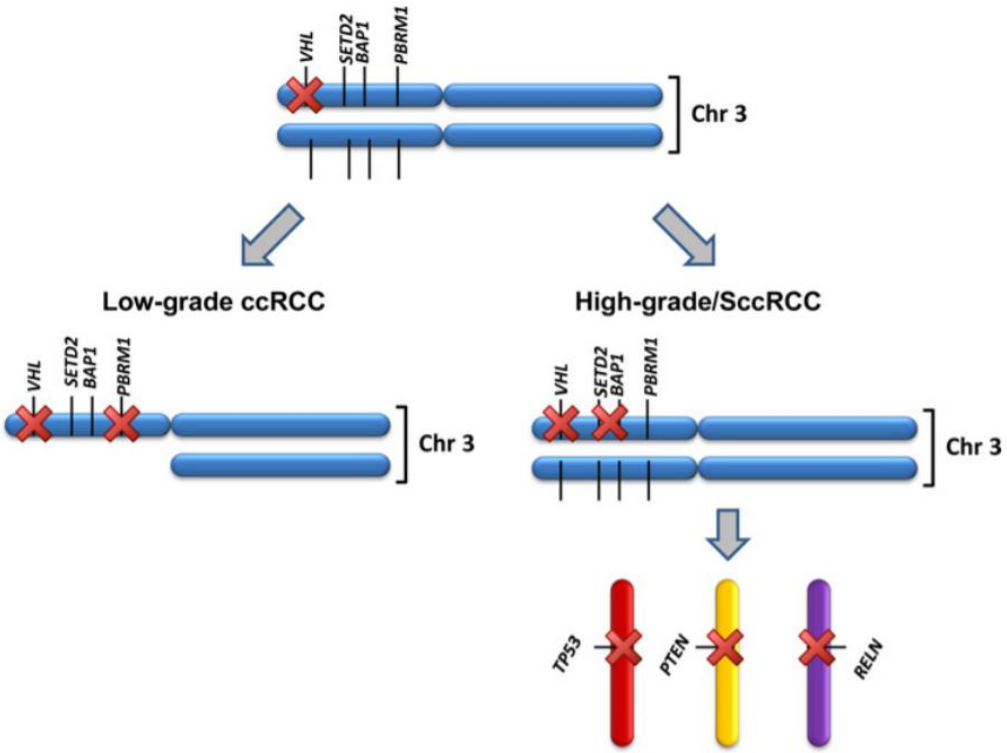



*Figure 3. Distinct molecular pathogenesis for low grade ccRCC and sarcomatoid RCC(20)*

## Syndromes associated with RCC

The most common inherited renal tumour syndrome is von Hippel–Lindau (VHL) syndrome. Other hereditary tumor syndromes include hereditary papillary renal cell carcinoma (HPRCC), Birt–Hogg–Dube (BHD) syndrome, hereditary leiomyomatosis renal cell carcinoma (HLRCC), succinate dehydrogenase renal cell carcinoma (SDH-RCC), tuberous sclerosis (TS), and Cowden's disease which are caused by alterations of other genes, including MET, FLCN, FH, SDHB, SDHD, TSC1, TSC2, and PTEN. (17)

## Significance of radiology:

The widespread use of modern diagnostic imaging techniques, especially computed tomography and sonography, has led to the detection of an increasing number of

serendipitous renal neoplasms, with the patient showing no signs nor symptoms related to the neoplastic renal disease.(21)

Renal masses unrelated to the presenting complaints are common incidental findings. Although most incidental renal masses are benign, most of the renal cell carcinomas are identified initially as incidental findings. It is more important in an aging population where the frequency of encountering renal incidentalomas is increasing due to the rise in prevalence of renal cysts and renal cell carcinoma with age. (22)

Renal masses, including benign and malignant are mostly discovered incidentally when an imaging is done to evaluate a non-renal complaint. Therefore, differentiating incidental benign renal masses from those that are potentially malignant is important.(23,24)

RCCs exhibit a variable spectrum of morphologic appearances ranging from small indolent lesions to large aggressive masses associated with local invasion and metastatic disease. Despite the wide range of findings that are encountered, careful attention to certain imaging characteristics can be helpful in discriminating between the subtypes.

The gross morphologic profile of the tumor can provide clue towards its subtype.

Clear cell RCC may exhibit exophytic growth and have a tendency to be heterogeneous due to intra-tumoral necrosis, cystic change or hemorrhage.

Seventy percent of papillary RCCs are confined to the kidney at presentation and are generally small in size (≤ 3 cm) and low grade, manifesting as peripherally located tumors which are well-circumscribed and homogeneous. Papillary tumors if > 4 cm can show internal heterogeneity due to cystic change and necrosis.

Papillary RCCs with extensive cystic changes may show hemorrhagic fluid content and internal mural nodules or papillary projections while clear cell RCCs with cystic features typically show clear fluid content, irregular walls and septations. Calcifications are significantly more frequent in papillary RCCs (32%) and chromophobe RCCs (38%) than clear cell RCCs (11%).(25)

The signal intensity appearance of the tumor on T2 weighted MRI is an important imaging characteristic. Intratumoral hemosiderin deposition, as observed histologically with papillary RCC, correlates to the low signal intensity on T2-weighted images, in contrast to most clear cell RCCs which show high T2 signal intensity.(26)

CT perfusion is another advanced technique that calculates quantitative parameters which reflect the tumor's intrinsic microvascular environment such as blood flow, blood volume, capillary permeability and mean transit time. This may have a potential role as a prognostic marker as a greater microvascular density is associated with improved prognosis and longer survival for RCC

$^{18F}$-fluorodeoxyglucose positron emission tomography (PET)-CT is another newer modality that has been used to evaluate RCC. It is found that clear cell RCCs have significantly higher maximum standardized uptake and tumor-to-normal tissue ratio than non-clear cell RCCs when evaluated during the early dynamic phase. However, PET-CT has limited primary tumor assessment significance, as physiologic tracer excretion by the kidneys can mask an RCC, leading to false negative results. Hence PET-CT has more of a significant defined role for disease re-staging in advanced RCC and in recurrent RCC. (25)

With the possible exception of an adipose-rich angiomyolipoma, there are no clinical or radiologic features that can accurately predict the histologic subtype of a renal mass. Establishing the diagnosis has traditionally relied on the removal of the renal mass.(27)

The possible advantage of all these imaging modalities is that the tumor size at presentation decreased as they were radiologically picked up before the patient became symptomatic.(28)

Incidentally detected renal cell carcinoma has a significantly better prognosis than symptomatic tumors. Having progressed to a point at which they clinically manifest, symptomatic tumors are more aggressive and present at a significantly higher stage and grade than incidental lesions. Subsequently incidental lesions have a better overall survival with lower recurrence and metastasis rates.(29)

## Histological classification:

## Evolution of classification of renal cell neoplasms:

The classification of renal epithelial neoplasia has undergone much changes over the past 3 decades mainly due to the advances in our understanding of basic morphology, immunohistochemistry (IHC), cytogenetics and molecular pathology. This has led to an expansion in the number of distinct tumor entities that are recognized currently.

Heidelberg in 1996 and Rochester in 1997 were the two international consensus conferences that provided the basis for much of the last World Health Organization (WHO) renal tumor classification, which appeared in 2004.(30)

According to the 1997, Heidelberg classification there were only 4 subtypes and now it has increased upto12 recognized subtypes and several provisional entities as per the recent 2016 World Health Organization (WHO) Classification.(31)

The classification of renal cell neoplasia was routinely morphology based; but this has slowly changed over the last 35 years with the incorporation of genetic characteristics into the diagnostic features of some tumors. Although it was almost two centuries before that the earliest confirmed case of renal carcinoma was reported, it is only over the past three decades that we have come to an understanding that renal cell tumors represent a morphologic spectrum that differ in their architecture, genetics, and clinical behavior. (32)

The histological diversity associated with renal cell carcinoma was always known and also acknowledged in the 1975 AFIP Fascicle, Atlas of tumour pathology, second series on “Tumours of the kidney, renal pelvis and ureter”.

The two types described then were clear cell carcinoma and granular cell carcinoma. (9).

The 1981 WHO Renal Tumor Classification failed to thoroughly recognize the various benign and malignant morphological subtypes of renal cell neoplasia that had been reported then.

Thoenes et al. in their renowned study, classified the various RCC morphotypes that were then known and related them to the tissues of origin within the nephron. It was also noted that each of those morphotypes of RCC could have eosinophilic and spindle cell/pleomorphic variants, which resulted in the Mainz classification.

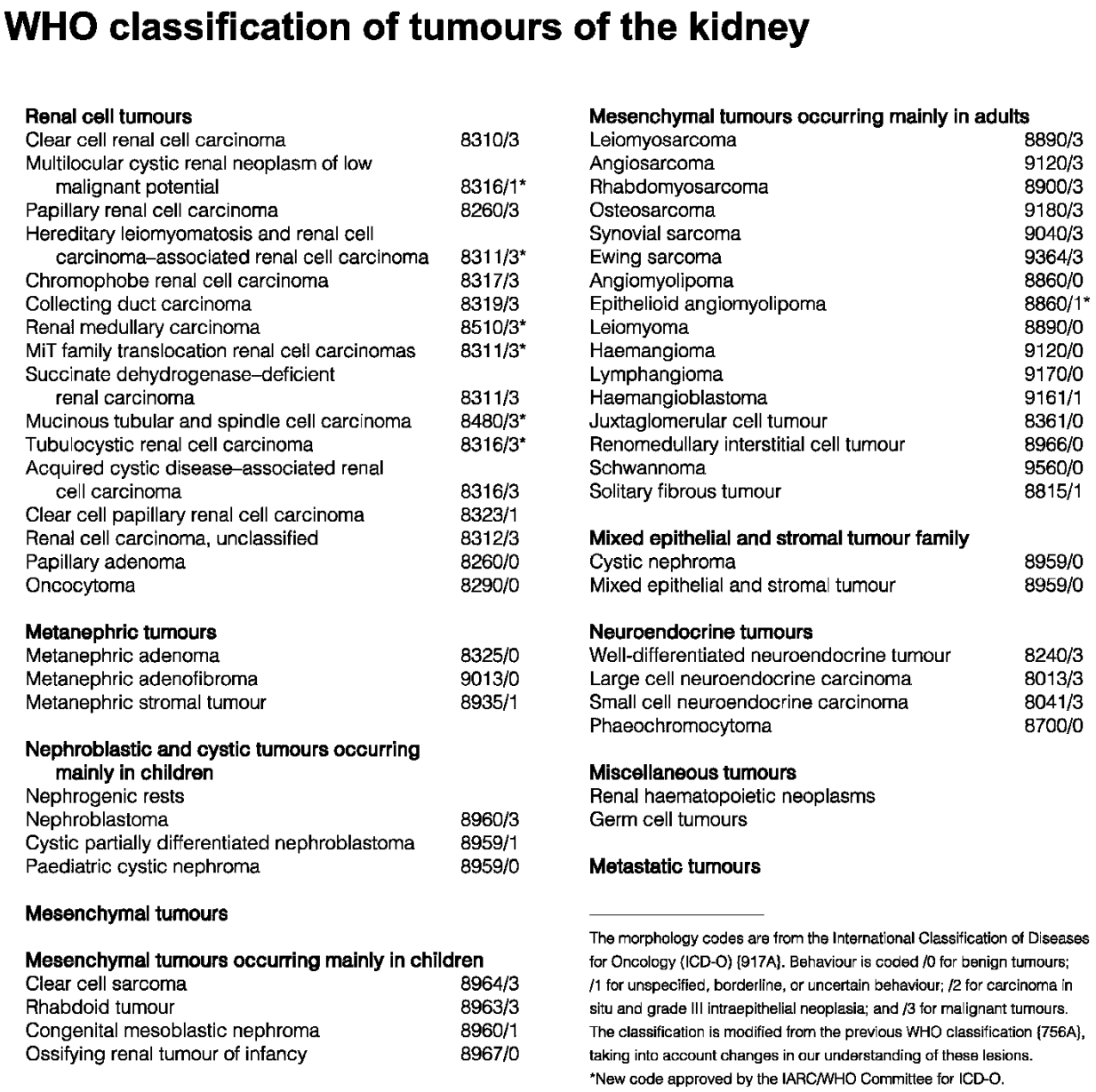
Hamburg in 1989, hosted a conference to formulate the second WHO Renal Tumor Classification, while the publication was delayed until 1998. This adopted a few features of the Mainz Classification but failed to recognize that neither granular cell nor spindle cell RCC as a distinctive morphotype of RCC. Subsequently two meetings were convened independently to provide for a classification of RCC as the 1989 one was a failure in explaining the pathogenesis of RCC. The first of these at Heidelberg in 1996, focused upon the genetic characterization followed by the next at Rochester, Minnesota, in 1997 which focused upon morphology. The resulting classifications were almost similar and are now known collectively as the Heidelberg/Rochester Classification.

The Heidelberg/Rochester Classification was expanded by the third WHO Renal Tumor Classification that was formulated in Lyon, December 2002.

After the third edition of the WHO Classification was published, several other new entities have been described along with changes in the diagnostic criteria for a number of recognized entities. In view of all these advances, the International Society of Urological Pathology convened a consensus conference in Vancouver in 2012 to formulate an updated classification of renal neoplasia.(32)

The International Society of Urological Pathology (ISUP) is an international professional organization which is solely dedicated to the subspecialty of urological pathology. The Society is recognized as an international reference authority and since its establishment 20 years ago has undertaken a major role in formulating reporting

standards for urological and male genital tract tumors.



## WHO classification of tumours of the kidney

| | |
|---|---|
| **Renal cell tumours** | |
| Clear cell renal cell carcinoma | 8310/3 |
| Multilocular cystic renal neoplasm of low malignant potential | 8316/1* |
| Papillary renal cell carcinoma | 8260/3 |
| Hereditary leiomyomatosis and renal cell carcinoma–associated renal cell carcinoma | 8311/3* |
| Chromophobe renal cell carcinoma | 8317/3 |
| Collecting duct carcinoma | 8319/3 |
| Renal medullary carcinoma | 8510/3* |
| MiT family translocation renal cell carcinomas | 8311/3* |
| Succinate dehydrogenase–deficient renal carcinoma | 8311/3 |
| Mucinous tubular and spindle cell carcinoma | 8480/3* |
| Tubulocystic renal cell carcinoma | 8316/3* |
| Acquired cystic disease–associated renal cell carcinoma | 8316/3 |
| Clear cell papillary renal cell carcinoma | 8323/1 |
| Renal cell carcinoma, unclassified | 8312/3 |
| Papillary adenoma | 8260/0 |
| Oncocytoma | 8290/0 |
| **Metanephric tumours** | |
| Metanephric adenoma | 8325/0 |
| Metanephric adenofibroma | 9013/0 |
| Metanephric stromal tumour | 8935/1 |
| **Nephroblastic and cystic tumours occurring mainly in children** | |
| Nephrogenic rests | |
| Nephroblastoma | 8960/3 |
| Cystic partially differentiated nephroblastoma | 8959/1 |
| Paediatric cystic nephroma | 8959/0 |
| **Mesenchymal tumours** | |
| **Mesenchymal tumours occurring mainly in children** | |
| Clear cell sarcoma | 8964/3 |
| Rhabdoid tumour | 8963/3 |
| Congenital mesoblastic nephroma | 8960/1 |
| Ossifying renal tumour of infancy | 8967/0 |
| **Mesenchymal tumours occurring mainly in adults** | |
| Leiomyosarcoma | 8890/3 |
| Angiosarcoma | 9120/3 |
| Rhabdomyosarcoma | 8900/3 |
| Osteosarcoma | 9180/3 |
| Synovial sarcoma | 9040/3 |
| Ewing sarcoma | 9364/3 |
| Angiomyolipoma | 8860/0 |
| Epithelioid angiomyolipoma | 8860/1* |
| Leiomyoma | 8890/0 |
| Haemangioma | 9120/0 |
| Lymphangioma | 9170/0 |
| Haemangioblastoma | 9161/1 |
| Juxtaglomerular cell tumour | 8361/0 |
| Renomedullary interstitial cell tumour | 8966/0 |
| Schwannoma | 9560/0 |
| Solitary fibrous tumour | 8815/1 |
| **Mixed epithelial and stromal tumour family** | |
| Cystic nephroma | 8959/0 |
| Mixed epithelial and stromal tumour | 8959/0 |
| **Neuroendocrine tumours** | |
| Well-differentiated neuroendocrine tumour | 8240/3 |
| Large cell neuroendocrine carcinoma | 8013/3 |
| Small cell neuroendocrine carcinoma | 8041/3 |
| Phaeochromocytoma | 8700/0 |
| **Miscellaneous tumours** | |
| Renal haematopoietic neoplasms | |
| Germ cell tumours | |
| **Metastatic tumours** | |

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) (917A). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification (756A), taking into account changes in our understanding of these lesions.
*New code approved by the IARC/WHO Committee for ICD-O.

*Figure 4. WHO classification of renal tumors (2016)(33)*

There has been a drastic change with interesting findings in the different morphological subtypes of adult renal epithelial neoplasia with many unique variants, each with its own characteristic histological features, immunoprofile and molecular characterization.

Further study has proved that histological classification was merely not just a futile academic exercise but it also helped in stratifying these tumours prognostically**.**

Clear cell renal cell carcinoma:

Clear cell RCC (ccRCC) is the most-common subtype of RCC. It has a moderate male predilection and typically occurs as a solitary, solid, and/ or cystic cortical mass in elderly.

Genetics:

Clear cell RCC is associated with sporadic alterations in, and subsequent loss of heterozygosity of, the von Hippel-Lindau tumor suppressor gene.

VHL syndrome is the genetic predisposition to the development of ccRCC which is associated with germline VHL mutations. These are characterized by numerous, bilateral ccRCCs beginning at an early age and may also develop paragangliomas, pancreatic tumors, hemangioblastomas, endolymphatic sac tumors and papillary cystadenomas of the epididymis/ broad ligament.

Morphology:

The classic morphologic features include abundant optically clear cytoplasm; nested, trabecular, and/or alveolar architecture; and a branching (‘‘racemose’’) network of thin walled vessels. It is the low grade tumours that display these classic features. On the other hand high-grade ccRCC show features of granular to eosinophilic cytoplasm, papillary/pseudopapillary architecture, and sarcomatoid/rhabdoid features.

Immunohistochemistry:

Typically these tumours express pancytokeratin, epithelial membrane antigen, CD10, and carbonic anhydrase IX. CK7 expression is usually negative or focal.

Morphologically, diagnosis of these tumours is pretty straightforward. Prognostically, there are two entities in the differential diagnosis of ccRCC which are important because they have an indolent course. These include multilocular cystic renal neoplasm of low malignant potential and clear cell papillary RCC (ccPRCC).

Multilocular cystic renal neoplasm of low malignant potential:

Multilocular cystic RCC was the older name prior to the current 2016 WHO classification where it is now classified as multilocular cystic renal neoplasm of low malignant potential, as there has been no evidence of recurrence or metastasis with long term follow up although they share a few molecular alterations with clear cell RCC. But they initially have to be strictly diagnosed using the given morphologic criteria.

Grossly, it is a cystic, cortical mass which is composed of numerous multiloculated cysts which are lined by cells that have clear cytoplasm and small, round nuclei with inconspicuous nucleoli (ISUP nuclear grade 1 or 2); and with intervening thin, fibrous septae separating the cysts and contain scattered ‘‘nonexpansile’’ nests of clear cells.

The differential diagnosis from clear cell carcinoma is resolved purely on morphologic grounds, with the lack of expansile nests of tumor cells within fibrous septae being the key feature. It is strongly recommended to submit all tissue from the specimen before signing out a diagnosis of multilocular cystic neoplasm of low malignant potential.

Clear cell papillary RCC

Clear cell papillary RCC is yet another new entity described in the 2016 WHO classification.

It is a sporadic tumour though once upon a time it was associated with patients with end-stage renal disease. It has no sex predilection and a very good prognosis. But in contrast to multilocular cystic renal neoplasm of low malignant potential, ccPRCC is a distinct molecular entity in itself as it does not share any common molecular alterations with ccRCC.

Clear cell papillary RCC typically presents as a small, circumscribed, solid and/or cystic cortical mass.

The tumour is composed of cells with optically clear cytoplasm and often demonstrating a papillary architecture, although it can display other patterns like cystic, solid, acinar, and tubular architecture.

The neoplastic cells have clear cytoplasm with low nuclear grade (ISUP grade 1 or 2). The existence of cases of ccPRCC of higher nuclear grade is not well established curently, although it is certainly possible. One characteristic feature of this tumor is the linear arrangement of the nuclei away from the basal aspect, toward the middle or the apex of the cells. Foamy macrophages, tumor necrosis, and vascular invasion are not seen.(30,31)

Immunohistochemistry is distinctly different from ccRCC in that ccPRCC is strongly and diffusely positive for CK7 and CA-IX displays a diffusely positive but characteristic basolateral (‘‘cuplike’’) membranous staining pattern, with a relative lack of staining at the apical membrane.(31)

Cases with typical morphology, but without the typical IHC profile, cannot be definitively placed in this tumor category. The main differential diagnosis of ccPRCC is with clear cell RCC. Some clear cell RCCs may have foci resembling ccPRCC and may even show CK7 positivity, but such positivity is only focal. Unlike ccPRCC, they are also CD10 positive. At the molecular genetic level, ccPRCCs lack deletions of 3p25, VHL gene mutations or VHL promoter hypermethylation. The number of cases in the literature with extended clinical follow-up information is small; however these neoplasms behave indolently.(30)

Intratumoural heterogeneity in ccRCC:

One of the major complications in developing effective therapies is that individual tumors are often genetically heterogeneous. It was shown that intratumoral heterogeneity leads to an underestimation of the genomic landscape of the tumour as it is often portrayed in a single biopsy sample and also for the fact that primary tumors and consecutive metastases may have different molecular alterations. Epigenetic events are also likely to be heterogeneous within a tumor.(17)

Many of the mutations which were initially perceived to be cancer drivers were later found to be present only in a segment of each tumor. The genesis of later mutations observed in the different regions appeared to be different from the mechanisms that were postulated to be responsible for the early genetic events. The clinical significance of this being that tumor heterogeneity may affect and possibly confound, targeted therapeutic interventions.

VHL gene mutation along with chromosome 3p loss was found universally in all samples from every tumor and it was considered to be the ‘truncal’ mutation as they

were present early in the genomic phylogenetic tree. Truncal mutation of the chromatin remodeling gene PBRM1 was also found in a subset of tumors. Conversely, other driver mutations— including alterations in the chromatin-remodeling genes SETD2, BAP1 and KDM5C, the TP53 gene and genes in the phosphoinositide 3-kinase (PI3K)-mTOR pathway (PTEN, PIK3CA, TSC2 and MTOR)—were found to be present only in segments of the tumor and were labeled 'branch' mutations. Each assessed portion of tumor was found to have a unique spectrum of branch mutations.

In a study by Gerlinger et al. it was found that, as more areas were sampled, more heterogeneity in the tumour was identified, which suggested that we might be underestimating the true extent of genomic heterogeneity in clear cell RCC.(34)

Single tumour biopsies do not portray the genomic landscape of a tumor well enough and hence could not be used to make decisions regarding individualized therapy. Although multi-region sampling might improve the predictive accuracy of biopsies, it is clinically impractical. (35)

## Papillary renal cell carcinoma:

It was not until 1976 that the pathological and clinical features of papillary renal cell carcinoma was first described.

Papillary RCC is the second most common subtype of renal cancer and occurs in approximately 10-16% of cases. Synchronous bilateral and multifocal cases of papillary tumors are observed in approximately 10% of cases.

Grossly, these tumors exhibit a solid or a mixed cystic/solid consistency. Papillary RCC lesions are often red-brown and frequently display a well-demarcated pseudo capsule if small.

Microscopically, these tumors have papillary or tubulo-papillary architecture. Calcifications, necrosis, and foamy macrophage infiltration are common histologic features.(15)

The neoplastic epithelial cells line delicate fibrovascular cores in which aggregates of foamy macrophages can be found. Sarcomatoid dedifferentiation is seen in approximately 5% of cases.

Two morphologic types of papillary RCC have been described.

Type 1 tumours are frequently multifocal and have papillae covered by small cells with scanty cytoplasm, arranged in a single layer on the papillary basement membrane with low nuclear grade.

Type 2 tumours are composed of cells with higher nuclear grade, eosinophilic cytoplasm, and pseudostratified nuclei on papillary cores.

Papillary RCC entirely composed of oncocytes also has been described.(36)

A higher proportion of papillary renal cell carcinomas was localized to the renal parenchyma at the time of diagnosis and the lower-stage tumors had a higher 5-year survival rate when compared to the ccRCC of the same stage.(37)

## New subtypes:

Five new tumour types have been recognized in the Vancouver classification. They are MiT family translocation RCC, acquired cystic disease-associated RCC, clear cell papillary RCC, hereditary leiomyomatosis RCC carcinoma syndrome-associated RCC and tubulocystic RCC.

Emerging variants:

Thyroid-like follicular RCC, succinate dehydrogenase β mutation-associated RCC and *ALK* translocation RCC were recognized as emerging tumor entities as there was insufficient information then available to permit their inclusion in the Vancouver Classification. (32)

Prognostic factors:

The prognosis of renal cell carcinoma is varying as it is a heterogeneous disease. Individual risk of disease progression and mortality after treatment is essential so that it will be helpful towards counselling patients, follow individualized surveillance protocols and help choose patients for individualized treatment schedules and also in participation of new clinical trials.

The prognostic factors which have been established for non-metastatic RCC are based upon anatomical, histological, clinical and molecular features.

Anatomical features that have been of use in the prognostication of RCC include the size of tumour, growth of tumor beyond the renal capsule, invasion of renal vein and/or inferior vena cava, lymph node invasion and metastases to distant organs.

As a general rule, RCCs which have a higher T stage, lymph node metastasis or distant metastasis are associated with worse prognosis and shorter survival periods.

T1 tumours were stratified into two subgroups (T1a and T1b) based on a cut-off in tumor size at 4 cm and this was first introduced in the 2002 TNM classification and subsequently its utility has been validated.

The histological features include Fuhrman nuclear grade which has been used for a long time, histologic subtype, presence of sarcomatoid component, micro-vascular invasion, tumor necrosis and collecting system invasion.

Clinical prognostic features include the performance status, local symptoms, cachexia and anemia.

Other factors with prognostic significance include the presence or absence of clinical symptoms at presentation.

The biggest breakthrough in prognostic factors comes in the form of molecular features and that is owing to the translational research done in the last decade which has provided us with great insight into the biological mechanism leading to the development and progression of RCC.

Vascular endothelial growth factor (VEGF) is associated with a more aggressive tumor phenotype and therefore a raised VEGF expression is significant. High carbonic anhydrase 9 (CAIX) is associated with a good prognosis.(38)

## Tumour size:

Tumor size, is one of the proven and useful prognostic factors in case of RCC and it forms a significant part of the current TNM staging system. It also guides in the selection of appropriate candidates for partial, open, laparoscopic, or robotic nephrectomy. Active surveillance of the tumours is also been guided by the tumor sizes assessed through various imaging modalities.

Hence, radiographic size of tumor continues to be an important factor in the era of minimal invasive treatment and this is based on the assumption that radiographic and

pathologic tumor sizes are equivalent. Findings have showed good efficacy across CT, MRI and ultrasound.(39,40) Though the actual size of the renal tumour can be generally overestimated by CT images, the difference is minimal and almost always clinically insignificant.(39)

Small renal masses are associated with an overall low risk of metastatic potential. Studies have also found that with each 1-cm interval increase in the tumor size there was a 20% concomitant increase in the risk of metastatic potential in renal cell carcinoma after surgery and for each 1-cm increase in the tumor size there is an increased risk of death from renal cell carcinoma by 10%. This proved that there is a very low risk of synchronous metastatic disease in case of small renal tumours.(41)

## Renal vein & IVC involvement:

RCCs that form venous thrombus are in general large, aggressive tumors displaying a higher nuclear grade including sarcomatoid features with a propensity for metastasis, thereby associated with poor prognosis. However, no difference was seen between RCC with renal vein involvement and RCC with IVC involvement when these same characteristics were compared. This might point towards the fact that tumors with different levels of venous involvement have similar biology and simply represent RCC diagnosed at different points in the course of disease progression(42)

Invasion of the venous system, with extension into the renal vein (RV) and the inferior vena cava (IVC) which occurs in 23% and 7% cases, respectively is one of the characteristic features of renal cell carcinoma. The prognostic significance of the level of venous extension is a matter of controversy.

In RCC with vein involvement, tumor size, perinephric fat invasion, lymph node and distant metastasis are important and independent prognostic factors while IVC invasion of any level significantly decreases the prognosis.(43)

Renal sinus:

Bonsib et al were the first to shine light on the potential significance of renal sinus invasion in the prognosis of RCC back in 2000. The hypothesis was that due to the lack of a capsule in the area of the sinus it would allow the tumors to have an easy access to the rich lympho vascular network of that region. This could also explain why a few localized RCC still metastasize.

This brought along a change in the tumour staging system as well. In 1997 American Joint Committee on Cancer/tumor-node-metastasis (AJCC/TNM) staging system failed to mention renal sinus invasion specifically. But in the following AJCC/TNM 2002 revision it was designated as part of pT3a disease. Specific sampling is required to document the presence or absence of this feature. Renal sinus fat invasion is especially more common when the size of the tumor exceeds 4 cm in diameter. It is so that with adequate and careful sampling pT2 category in itself becomes uncommon. (44)

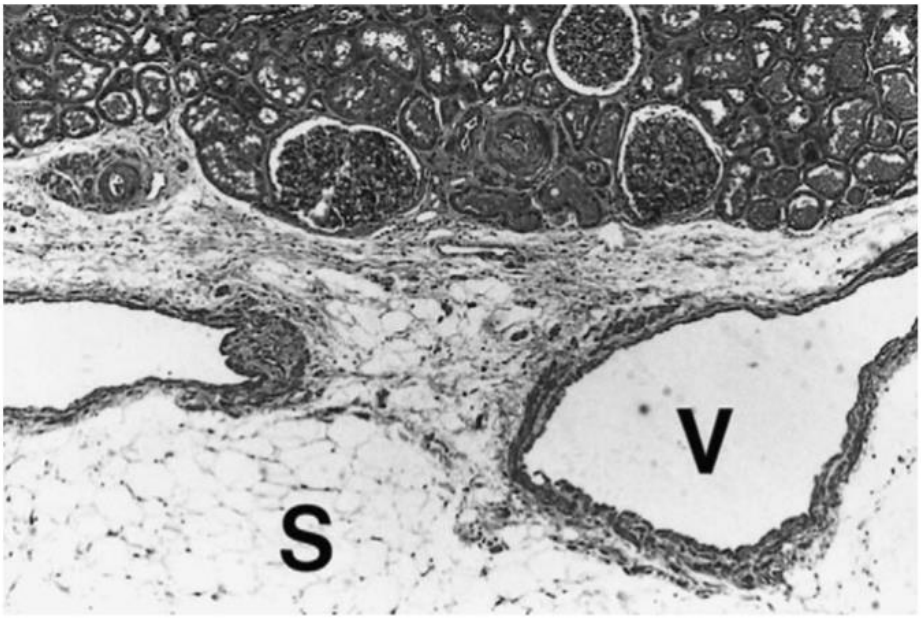



*Figure 5 Sinus fat devoid of capsule with an adjacent vein*

## Nuclear grading:

## Why grading?

Nuclear grading is important because they indirectly reflect on to the biochemistry of the malignant cells. When the malignant cells have an enlarged nuclei it reflects on DNA replication during cell cycle. Feulgen cytometry studies have confirmed the fact that tumors with a large, irregularly shaped nuclei have an abnormal, aneuploid complement of DNA. (45)

Broders in 1920 first proposed that tumours could be classified according to the degree of differentiation based on his study of squamous cell carcinoma of the lip. This was later applied to renal tumours by Hand and Broders in 1932 where they divided it into four grades. Grade 1, 75-100% differentiation to grade 4, 0-25% differentiation. But the drawback was that very few RCC contain differentiated foci

resembling renal tissue and hence Hand and Broder's grading system was not applicable to them.

Griffiths and Thackray in 1949 came up with a composite grading system with three grades and which included cell morphology, tumour architecture, degree of nuclear pleomorphism and mitotic rate as the criterias.(46)

Over 20 years passed before Skinner et al made several landmark observations in the grading of RCC. In a series of 309 patients uniformly treated by nephrectomy and followed up over a period of 6 years, they reported a significant association of 4 grades and 1-, 5-, and 10-year survival rates. Skinner and colleagues defined several histologic parameters in grading RCC, which still remain in use today. This was the first study to grade RCC on the basis of nuclear features alone and to define the grade of RCC on the basis of the highest-grade area within a tumor. They were also the first to associate the different subtypes with patient outcome. They defined tumors as pure clear, clear and/or granular, and spindle cell (sarcomatoid) and showed that patients with pure clear cell RCC had a significantly better outcome compared with patients with clear cell/granular tumors and that both did significantly better than patients with spindle cell tumors.(47)

Since then numerous other composite grading systems have been proposed but one recurring feature is their inability to stratify the importance of the grading criteria which would imply that each feature should be given an equal weighting when tumors are assessed.

Other drawbacks of composite grading systems include limited defining criteria, with grading based on what was described as overall microscopic appearance, or degree of

differentiation, thus promoting interobserver error. These errors are compounded by a failure of authors to clearly state if grading should be based on the highest grade, the average grade, or the predominant grade present within the tumor.

In the majority of studies, significance testing was undertaken with outcomes showing significant differences between grades. But in few studies, significance was only achieved when lower grades were pooled and tested against the highest defined grade.

Despite the prognostic significance of many of the proposed composite and nuclear grading systems, few fail to predict the survival in the majority of cases adequately. In most grading systems high- and low-grade tumors are associated with an unfavorable or favorable prognosis, respectively; however, the majority of RCCs in these studies have been classified into the intermediate grades where outcome is less predictable and in some classifications there was a lack of statistical significance when survivals of patients with tumors in these intermediate grades were compared.(46)

To date, more than 25 different grading classifications for RCC have been proposed.

## Fuhrman grading:

Fuhrman's 1982 report regarding the nuclear grading has been one of the most cited studies in the renal cancer literature. Despite this acceptance, the utility of the Fuhrman grading has been questioned and studies have highlighted problems relating to the application of the grading system.

It is a four point multi parametric scale which is based solely on the nuclear features which include—nuclear size, shape, chromasia and nucleolar prominence.(48) Other histological features like architecture and necrosis are not relevant in this system.

*Table 1. Fuhrman nuclear grading system (48)*

| Grade | Nuclear diameter | Nuclear Shape | Nucleoli |
|---|---|---|---|
| **Grade 1** | Small (~10 μm) | Round, uniform | Absent inconspicuous |
| **Grade 2** | Larger (~15 μm) | Round, uniform | Visible at x400 |
| **Grade 3** | Larger (~20 μm) | Obvious, irregular outline | Visible at x100 |
| **Grade 4** | As for grade 3 with bizarre multi lobed Nuclei ± spindle cells | | |

Fuhrman grading system was based on a composite series of tumors containing a variety of RCC subtypes, which included clear cell and papillary RCC. Survival analysis of the cases in their report showed that grading was significantly related to outcome over a 5-year follow-up period when grade 2 and 3 tumors which constituted about 76% of total cases were pooled into a single grade. Since then many different studies have investigated the prognostic significance of Fuhrman grading among a variety of morphologic parameters and have contained a mixed series of renal epithelial tumors. But all these studies are of limited validity as they fail to consider the confounding influence of the prognostic significance of tumor type.

Drawbacks of Fuhrman:

One of the drawbacks was that the Fuhrman system was not clear regarding the extent of the most atypical component of the tumor. There were concerns regarding the extent of sampling of the tumor to find the highest grade. (45)

It has been proven that neither Fuhrman grading, either for the whole tumour or focally, nor any of its individual components will be of any use as a prognostic indicator for chromophobe renal cell carcinoma. (49) It is also not applicable to Xp11.2 tRCC. (50)

There are numerous drawbacks of the Fuhrman grading system. As originally defined, the system is based on the simultaneous assessment of three parameters which include—nuclear size, nuclear pleomorphism, and nucleolar prominence, without any objective evidence of concordance between these parameters. In cases where there is a discrepancy between the different parameters no recommendation has been provided to indicate which grading parameter should be given importance when assigning a grade in individual cases. Some pathologists attempt to skip this issue by confining grading to assessment of nucleolar prominence alone, and thereby ignoring the other two parameters as defined by Fuhrman.

The criteria for nuclear pleomorphism are poorly defined and features relating to nucleolar prominence are subject to inter-observer error as per the Fuhrman system. In particular many nucleoli visible at x400 magnification are visible at x100, and the decision as to whether these are sufficiently prominent at the lower magnification to justify an assignment of grade 3 is left to the individual pathologist's discretion. The uncertainty relating to the assessment of these criteria is reinforced by the fact that

there is only fair to at-best moderate inter-observer and intra-observer reproducibility for Fuhrman grading. Further evidence of the poor reproducibility of Fuhrman grading could be inferred from the observation that the number of cases within each grade varies widely between reported series.(46)

Numerous grading systems have been proposed for renal cell neoplasia but not all have been validated for the different morphological subtypes that have been described. However the one that is used widely is the one proposed by Fuhrman et al which has many drawbacks concerning its interpretation, validation and reproducibility. This led on to the new ISUP grading system which has been validated as an indicator for prognosis especially with clear cell renal cell carcinoma and papillary renal cell carcinoma.

For the other variants, the ISUP grading can still be used to describe the morphological feature but not validated as a prognostic marker. This has been mainly due to the fact that not much cases have been studied with those variants.(1)

Studies demonstrate that Fuhrman cannot be applied in more than 20% of cases of ccRCC and the WHO/ ISUP provides a better prognostic information. The application of WHO/ISUP grading also resulted in a general down-grading of cases when compared with the Fuhrman grading. (51)

Nucleolar grading:

*Table 2. ISUP grading(52)*

| Grade | Parameters |
|---|---|
| Grade 1 | Nucleoli absent or inconspicuous and basophilic at x400 magnification |
| Grade 2 | Nucleoli conspicuous and eosinophilic at x400 magnification and visible but not prominent at x100 magnification |
| Grade 3 | Nucleoli conspicuous and eosinophilic at x100 magnification |
| Grade 4 | Extreme nuclear pleomorphism and/or sarcomatoid and/or rhabdoid differentiation and/or tumor giant cells |

This grading system was adopted for clear cell and papillary RCC at the 2012 International Society of Urological Pathology (ISUP), Vancouver Consensus Conference on Renal Cell Neoplasia, and was subsequently endorsed by the World Health Organization (WHO), being re designated as the WHO/ISUP grading system in the fourth edition of the WHO Bluebook, Classification of tumours of the urinary system and male genital organs.

Sarcomatoid and rhabdoid morphology:

Sarcomatoid carcinoma is not defined as a specifc morphogenetic entity of RCC but rather considered as a pattern of dedifferentiation, and it is a distinct tumor from other rare neoplasms such like sarcoma of the kidney.

This sarcomatoid de-differentiation happens to originate from epithelial–mesenchymal transition (EMT) which is a biologic process in which epithelial cells gradually go on to lose their epithelial phenotype and acquire a mesenchymal one, thereby displaying spindle cell morphology, increased motility, invasive capacity, high resistance to apoptosis and increased production of extracellular matrix proteins.(53)

Tumour cells with a sarcomatoid appearance denote high-grade morphology and are usually associated with poor outcome. Distant metastasis (45-77%) is usually found at the time of diagnosis and has approximate 5 year survival of 15–22%.

Grossly, areas of sarcomatoid differentiation appear as dense grey-white areas with invasive margins and a firm, fleshy to fibrous cut surface.

Microscopically, sRCC contains both epithelial (carcinoma) and mesenchymal (sarcomatoid) components, which is not the case in a true sarcoma.

Although any histological pattern can be seen, the most common pattern seen is a spindle cell sarcoma. This component can be present in any of the tumour types, altogether occurring in approximately 5% of cases.

There is no cut off for amount of sarcoma that needs to be visualised to record this component while tumours consisting of sarcomatoid component only are placed in the ‘unclassified’ category in the WHO classification. The extent of sarcomatoid morphology has been proven to adversely affect patient survival, but there is no international consensus yet on how this could be quantified and qualified reliably.

Patients who have more than 30% sarcomatoid component in the primary tumor frequently display sarcomatoid histology in a metastatic site.(53)

Rhabdoid morphology constitutes the presence of large atypical cells with eccentric nuclei which also is associated with a poor prognosis. Though it can occur in any of the RCC type, clear cell RCC is where it usually is seen.

At the molecular level, an association has been shown between the rhabdoid phenotype and alterations in the switch/sucrose non fermentable (SWI/ SNF) chromatin modelling complex, similar to that noted in aggressive carcinomas from other sites displaying a rhabdoid or undifferentiated phenotype.
Sarcomatoid and rhabdoid morphology may be seen concurrently and both of them are classified under WHO/ISUP grade 4. However, the presence of sarcomatoid morphology is shown to have a more significant association with death from RCC than the presence of rhabdoid morphology.(54)

## Tumour Necrosis:

Tumor necrosis is defined as the presence of microscopic coagulative tumor cell necrosis, which is characterized by homogeneous clusters and sheets of degenerating and dead cells.

A common hypothesis regarding the mechanism of tumor necrosis is that it arises in tumors with rapid tumor growth that outstrips its own blood supply.

Histologic tumor necrosis is a well established independent prognostic factor in renal cell carcinomas, particularly ccRCC. It is associated with tumours of higher grade and denotes worse prognosis.

PRCC is a variant that is more susceptible to necrosis because of its hypovascularity, and hence not necessarily associated with worse prognosis.

One potential pitfall in assessing the extent of tumour necrosis is that there is a tendency to sample viable tumour while taking sections for histological examination.

So, gross appearance must also be taken into account while estimating percent of tumor necrosis.

In high-grade carcinomas, tumour necrosis typically imparts a worse prognosis while histological subtype, grade, and stage determine the prognosis in low-grade carcinomas.(55)

The presence of TN represents an independent predictor for metastasis-free and overall survival in patients with clear cell and papillary RCC.(56)

## Lymph node dissection in renal cell carcinoma:

Renal lymphatic drainage is unpredictable due to the presence of many possible different lymphatic routes in normal retroperitoneal anatomy. Also local progression of the tumor is unpredictable mainly due to its neovascularization, blockage of lymphatic vessels by tumor cells, collateral lymphatic drainage and invasion of the tissue with different lymphatic drainage (eg, perinephric fat).

Typically, the most frequent lymphatic landing sites for tumour cells are paracaval, retrocaval and interaortocaval for the right kidney and para-aortic, preaortic and interaortocaval nodes for the left kidney. Interestingly, the ipsilateral renal hilar region shows lymph node involvement in less than 10 % of the cases.

Over the years, the incidence of nodal involvement has been on the fall, from >30% in historical series to 3.3% in the recent studies. This could be explained by the increased ability to diagnose tumors in their earlier stages and with subsequent lower risk of nodal involvement.

From a radiological perspective, the available technology accurately identifies only large lymph node metastases while patients with micrometastases in normal-sized nodes who actually might benefit from LND cannot be visualized by the recent techniques. Therefore, when using the available imaging technology, the absence of any evident lymph node metastasis should not preclude the performance of a regional LND.(57)

Although lymph node dissection is currently accepted as the most accurate and reliable staging procedure for the detection of lymph node involvement, its therapeutic benefit in renal cell carcinoma (RCC) is yet to be proven.

In patients with clinical T1a/bN0 with favorable clinical and pathological characteristics, LND does not offer any additional staging information and has no benefit in terms of cancer control, while it may be beneficial in high-risk patients which include clinical T3–T4, high nuclear grade, presence of sarcomatoid features or coagulative tumor necrosis. But if enlarged nodes are found on imaging or palpable during surgery, then LND seems justified at any stage. However, the extent of the LND remains a matter of controversy.(57,58)

## Treatment:

The treatment of renal cell carcinoma has changed a lot over the past 15 years. This is mainly down to the progress made in the field of surgical management of the primary tumor along with the increased understanding of the molecular biology and genomics of the disease have led to the development of new therapeutic agents.

The management of the primary tumor has changed due to the realization of the fact that margins around the primary lesion if free of tumour are sufficient to prevent local

recurrence, as well as the development of more sophisticated tools and techniques that increase the safety of partial nephrectomy. The management of advanced disease has altered even more drastically due to a whole lot of new drugs added to the clinician's armamentarium which target the tumor vasculature or that attenuate the activation of intracellular oncogenic pathways. (4)

In case of resectable RCC, the standard of care is always surgical excision either by partial or radical nephrectomy with a curative intent. By contrast, inoperable or metastatic RCC typically undergo systemic treatment with targeted agents and/or immune checkpoint inhibitors. Treatment decision is guided by various nomograms. Few of the key prognostic factors which have been identified, validated and adopted to guide and stratify patients with metastatic RCC for systemic treatment include performance status, time from the diagnosis to systemic treatment and blood levels of haemoglobin, neutrophils, platelets, calcium and lactate dehydrogenase.

## Surgery:

The clinical stage of the disease and the general condition of the patient determines the surgical treatment. Typically, it is reserved for localized disease, though both partial and radical nephrectomy can also be used with cytoreductive intent in patients with metastatic disease, especially with a substantial disease volume at the primary site but only a low burden of metastatic disease.

**Partial nephrectomy**

The goal in partial nephrectomy is to completely remove the primary tumour while at the same time preserving the largest possible amount of healthy renal parenchyma. It is mainly indicated for patient with T1 tumours and those patients with a normal

contralateral kidney (elective indication). Moreover, partial nephrectomy is absolutely indicated in patients with RCC who have only one kidney (anatomically or functionally), patients with bilateral synchronous RCC and in those with von Hippel-Lindau syndrome. Relative indications include conditions that can impair renal function which includes renal stones, hypertension, diabetes and pyelonephritis. This procedure offers advantage of a lower renal function impairment but equivalent oncological survival outcomes compared with radical nephrectomy in those with T1 tumours.

Laparoscopic partial nephrectomy (LPN) and robot-assisted partial nephrectomy (RAPN) are the main alternatives available to classical open partial nephrectomy (OPN). However, these are more appropriate in the context of treating more complex cases. LPN is generally reserved for small tumours (usually ≤4 cm in size) in patients without complex features as defined according to nephrometry systems (low- or intermediate-risk categories). RAPN seems to be significantly better than OPN when it comes to perioperative complications, estimated blood loss and hospital stay. However, transfusion rate, ischaemia time, estimated glomerular filtration rate change and early cancer outcomes are similar between the above two approaches. International guidelines recommended the use of both approaches according to the surgeon and patient preferences.

Partial nephrectomy can also involve a simple enucleation whereby there is entire sparing of the healthy parenchyma around the tumor. Classic enucleo-resection whereby a thin layer of healthy parenchyma is removed or polar or wedge resection whereby a wider excision of healthy parenchyma is performed are also viable options. A minimal tumour-free surgical margin following partial nephrectomy is essential to

avoid the increased risk of local recurrence. However upto 1–6% of cases have reported positive surgical margins regardless of the type of surgical technique used. (9)

Historically, a 1-cm rim of healthy parenchyma was recommended to allow optimal local tumor control. The width of the negative margin does not affect the local tumor control. In patients who had a positive margin, only 7% of the reoperated renal remnants had viable tumor. Hence, the width of the negative margin can be kept to a thin, uniform rim of normal parenchyma. Intraoperative frozen section analysis is not definitive and has limited clinical significance and hence can be omitted in the setting of complete gross resection.(59)

Haematuria, perirenal haematoma and urinary fistulas are the most common complications of partial nephrectomy procedures. Less frequent postoperative complications can be represented by acute renal impairment and infection.(9)

A contemporary ideal PN excises the tumor with a thin negative margin, precisely secures the tumor bed, and reduces global ischemia to the renal remnant with minimal complications.(59)

**Radical nephrectomy**

Classical radical nephrectomy includes the removal of kidney, perirenal adipose tissue, adrenal gland and regional lymph nodes. However, if tumour ≤5 cm in size and located at the inferior pole, the adrenal gland can be spared. Similarly, regional lymph nodes dissection can be reserved for patients with clinically positive nodes detected by CT or during the surgical procedure. Radical nephrectomy is also to be considered in cases with multiple small renal tumours or when the tumour extends into the

vasculature. In most patients with stage I and II tumours, radical nephrectomy is currently performed using a traditional laparoscopic approach while the open approach continues to remain the gold standard for the treatment of more complex cases.(9)

## Justification of our study:

Although renal cell carcinoma is widely prevalent in the west, this is not the case in our country. Despite the low incidence of this tumour, it continues to be responsible for more mortality due to its inherent propensity for haematogenous metastasis. There have not been many studies from India regarding renal cell carcinoma and even the ones studied, did not include large numbers.

Nuclear grading is one of the most important prognostic factors for renal cell carcinoma which determines the behaviour. Multiple grading systems have been used over the years and of all the grading systems that have been postulated Fuhrman nuclear grading had stood the test of time until recently in 2012 when the new ISUP grading was put forth and later accepted by the WHO in 2014.

Considering the fact that there have not been many clinico-pathologic studies regarding renal cell carcinoma and the absence of any literature on whether ISUP grading system is superior over Fuhrman grading and appropriate in the context of our Indian population, this study was undertaken.

# MATERIALS AND METHODS

This is a retrospective study, carried out in the Department of General Pathology. All cases which were diagnosed as clear cell renal cell carcinoma and papillary renal cell carcinoma over a period of three years were included in this study.

Inclusion Criteria:

- All adult cases of clear cell and papillary renal cell carcinoma from January 2013 to December 2015.
- Adequate follow up information (Minimum of one year).

Exclusion Criteria:

- Needle biopsies
- Pediatric age group
- All other variants of renal cell carcinoma
- Cases with no available paraffin blocks
- Cases with inadequate follow up information

All renal cell carcinomas of clear cell and papillary sub-type diagnosed in the Department of General Pathology in the time period January 2013 to December 2015 were retrieved from the electronic records and those that had paraffin blocks were retrieved from the archives of the General Pathology Department along with the corresponding stained slides.

The follow up information for each of these cases was ascertained from the clinical records database, and only cases with an adequate follow up period were included in the study.

Pediatric renal cell carcinomas, i.e. all the tumours occurring in <18 years of age were excluded from this study.

All other renal cell tumor subtypes were excluded from this study.

Slides of each biopsy were reviewed. Representative slides which showed the highest nuclear grade of the tumor were selected and sections cut from their corresponding paraffin blocks.

From the clinical database, all cases with a follow-up period of less than 12 months were excluded, unless a proven metastasis or death had occurred within the same time period.

## Clinical details of the cases:

The clinical details of these patients were obtained from the charts retrieved from the Medical Records Department and the Clinical WorkStation.

The following clinical details were sought:

- Age
- Sex
- Presenting complaints
- Family history
- Co-existing medical conditions
- Surgical procedure done
- History regarding recurrence/metastasis/ death.

Gross details:

- Type of nephrectomy (Partial/Radical)
- Location of tumor
- Size of tumor
- Hilar lymph nodes

Histological details:

The histological features of each of these cases was initially reviewed by the principal investigator. The morphological sub type of renal cell carcinoma (renal cell/ papillary) was established first. If it was papillary, further subtyping into papillary renal cell carcinoma type 1 or 2 was done. The primary aim was to grade these cases separately utilizing both the Fuhrman system and the ISUP grading.

The grading was initially done by the principal investigator and then followed by the guide and a third co-investigator.

Other histological parameters like the presence or absence of capsular and lympho-vascular invasion were also noted. Tumour necrosis was looked for and if present was graded either as <10%, 10-50% or >50%.

## Statistical methods:

Descriptive statistics for categorical predictors were given using frequency and percentage.

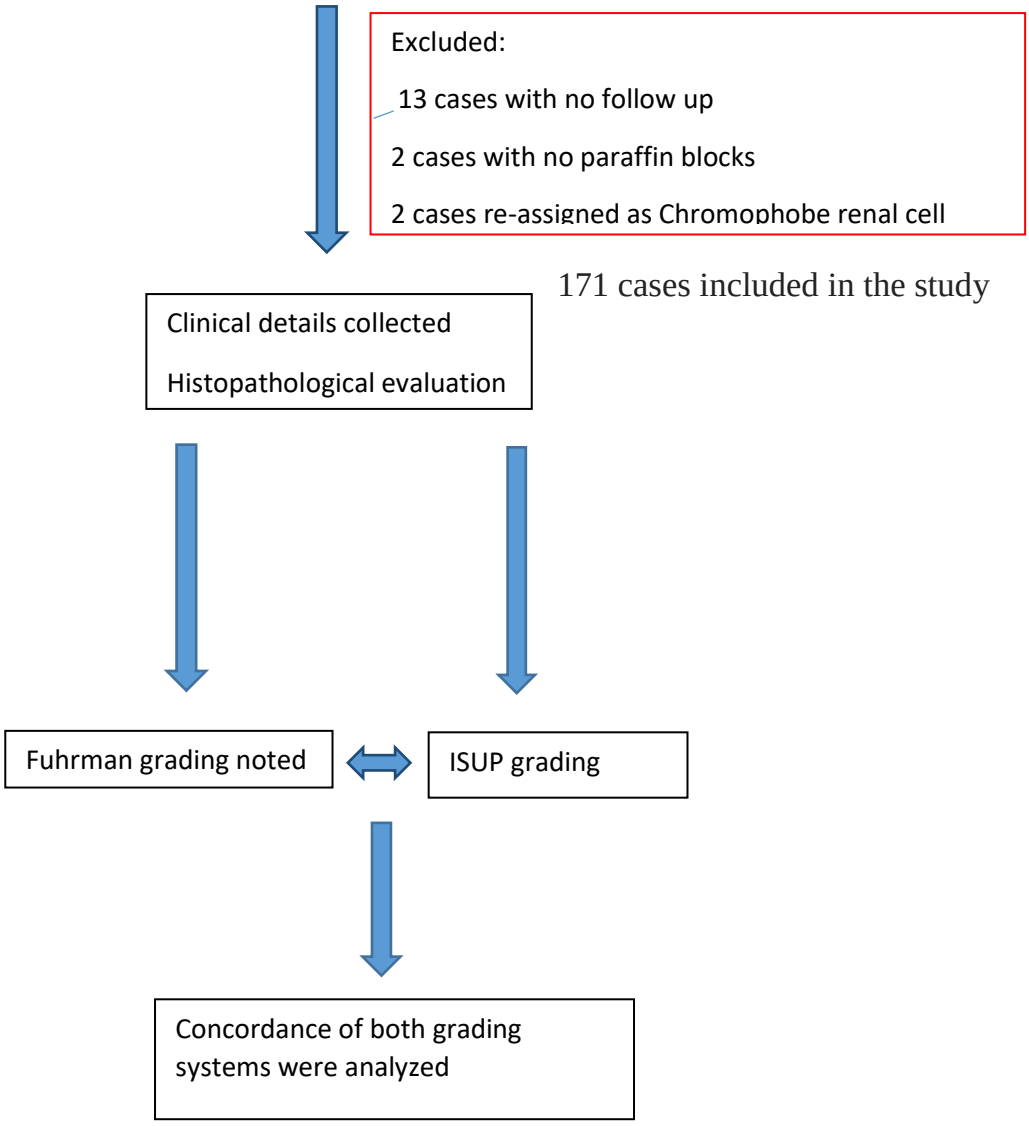
The agreement between two grading systems was assessed using weighted kappa. Kaplan-Meir estimate was used to assess the event free survival and progression in the two types of grading system. Univariate analysis, to find the predictors of recurrent event was assessed using log rank test. Cox-proportional hazard model was used for the multivariable analysis if the assumption satisfies.

The predictors which were significant in univariate analysis were taken for multivariate analysis and effect of the estimate was presented as hazard ratio (95% CI).

# RESULTS

Scheme of the study:

188 cases of adult clear cell and papillary renal cell carcinoma




Statistical results:

There were 188 cases of clear cell and papillary renal cell carcinoma that were diagnosed solely on morphological grounds over the period of study. Out of these, 13 cases had follow up period of less than a year while 2 cases did not have paraffin blocks. Upon systematic review of all the slides it was found that the morphology of 2 cases was inconclusive and favoured Chromophobe renal cell carcinoma and hence excluded.

## Demographic parameters:

Age:

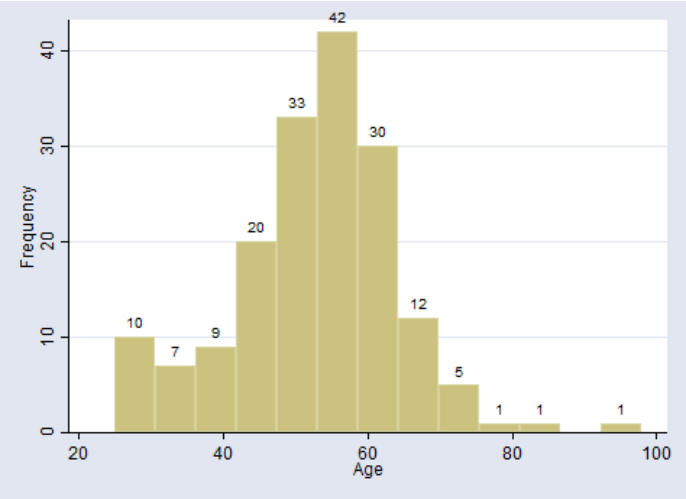



*Figure 6. Age distribution of the cases*

The mean age of presentation was 52.89 years with an overall range of 25 to 98 years. The distribution of tumours was more in the 5$^{th}$ to 6$^{th}$ decades of life. The youngest patient was 27 years old and was associated with VHL syndrome while the oldest was a 98 years old man.

Sex:

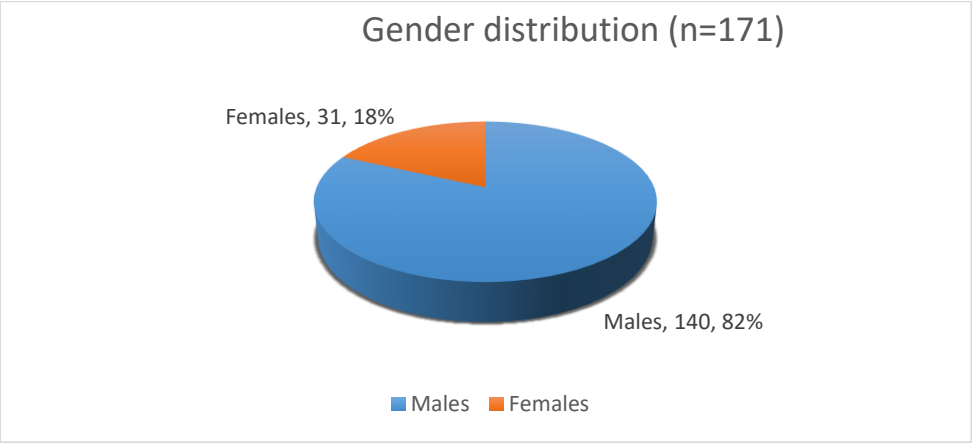



*Figure 7. Gender distribution of the cases*

Renal cell carcinomas are more common in males than in females, with a male: female ratio of 4.5: 1 (Males: 140, Females: 31).

Mode of presentation:

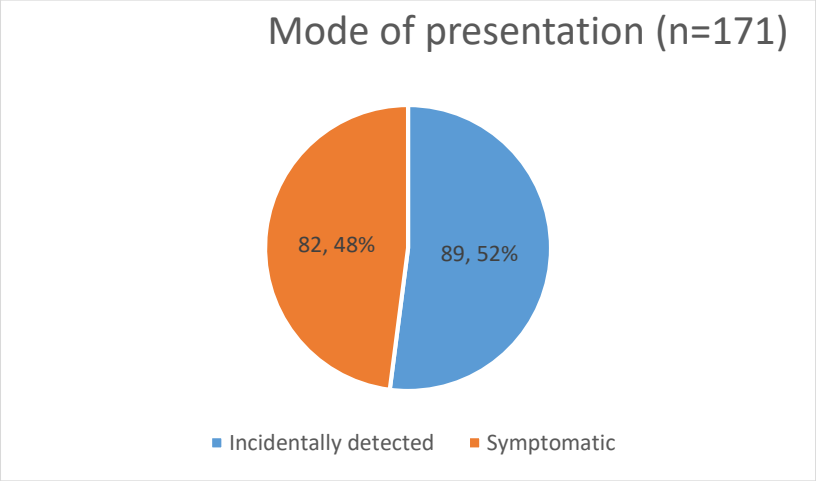



*Figure 8. Mode of presentation of the cases*

Based on the clinical history collected from the electronic medical records it was found that just more than half of the patients, 52% (n=89) had presented incidentally. They were completely asymptomatic and were detected incidentally, mostly by radiological investigations when they presented for other unrelated symptoms.

Presenting complaints:

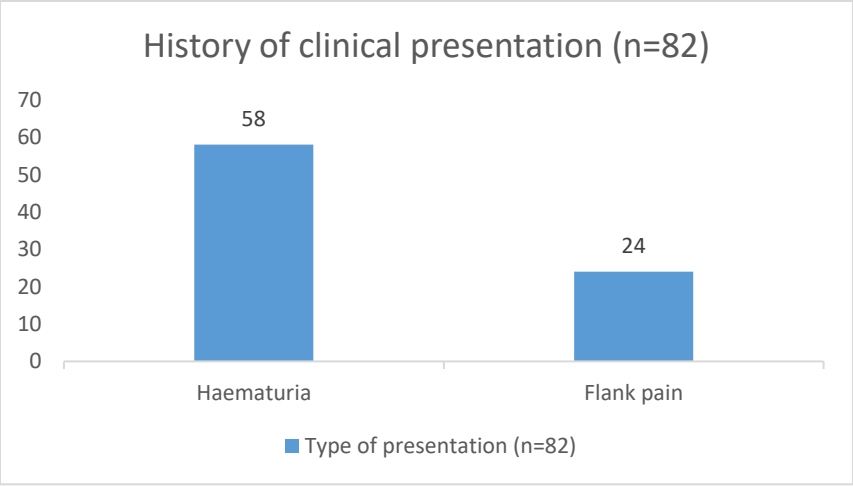



*Figure 9. Presenting complaints among the symptomatic cases*

Amongst the patients who presented with symptoms (n=82), haematuria was the commonest symptom seen in 71% patients (n=58), followed by flank pain seen in 29% patients (n=24). None of the patients presented with abdominal mass or with the classic triad of symptoms as described in literature.

Comorbidities:

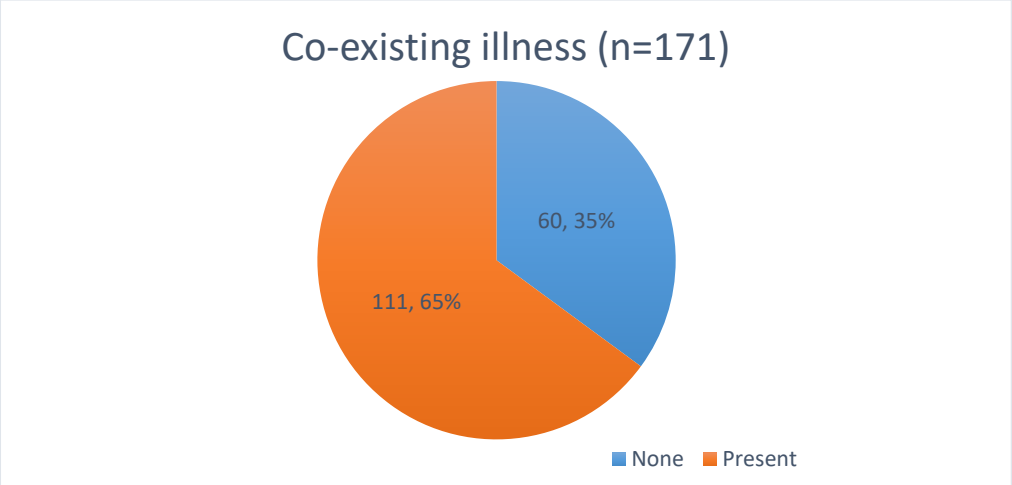



*Figure 10. Coexisting medical illness.*

Amongst171 patients, up to 65% (n=111) had some form of a co-existing medical illness, while the remaining were free from any co-existing illness.

Distribution of the various comorbidities:

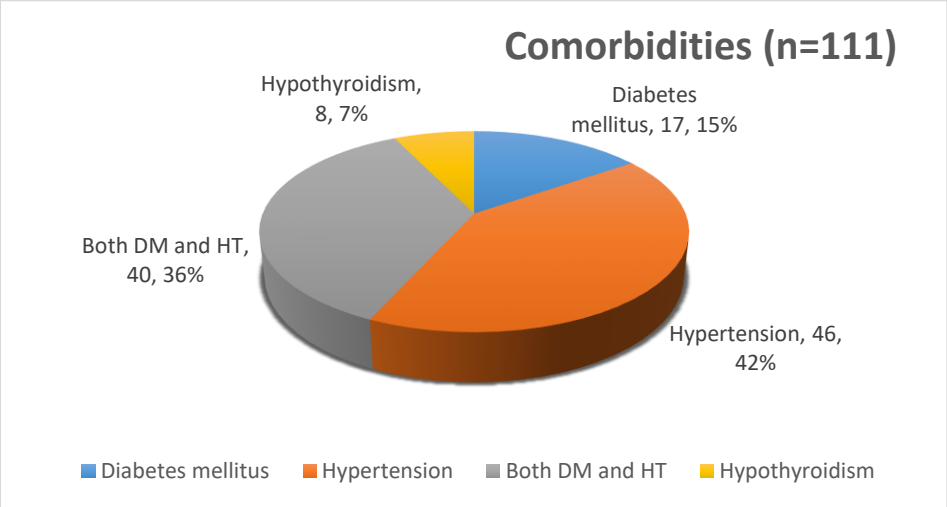



*Figure 11. Distribution of the concomitant medical conditions.*

Clinical details collected from the electronic records and medical charts revealed that among the 111 patients who had a co-existing medical illness, up to 42% (n=46) were purely hypertensive, 15% (n=7) were purely diabetic and 36% (n=40) had both diabetes and hypertension. About 8 patients (7%) had a history of hypothyroidism.

Side involved:

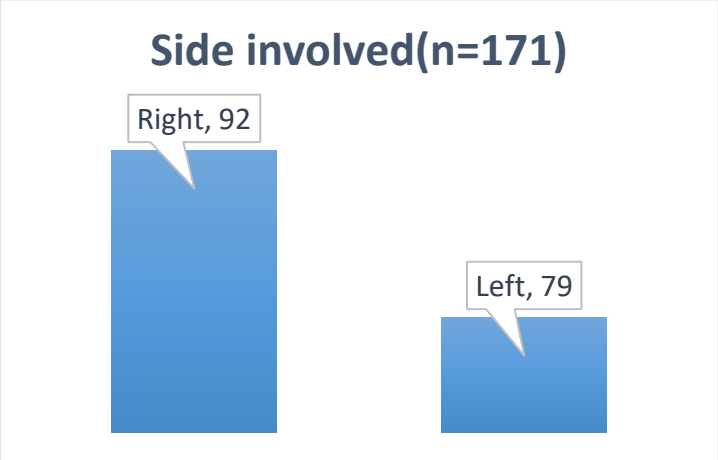



*Figure 12. Distribution of the side of tumour.*

The tumour distribution based on the side of the affected kidney is as follows -

Tumours were seen slightly more on the right side (54%) and the remaining 46% were on the left side. There were no bilateral tumours seen in our study.

Syndromic association:

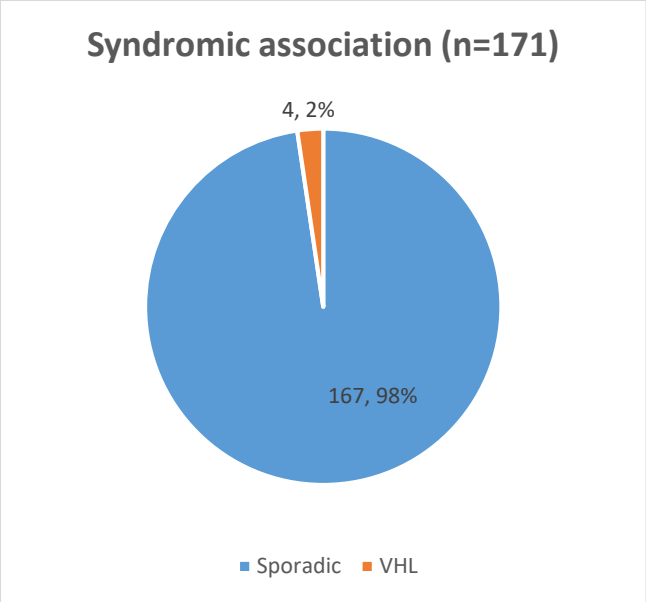



*Figure 13. Renal cell carcinomas associated with hereditary syndromes.*

There were four cases that were associated with an inherited genetic syndrome, all of which were VHL associated, forming 2% cases of renal cell carcinoma which were associated with syndromes.

*Table 3. Grading in the cases associated with VHL.*

| VHL cases | Age(Years) | Fuhrman grade | ISUP grade | Tumour necrosis |
|---|---|---|---|---|
| Case 1 | 27 | 2 | 1 | No |
| Case 2 | 28 | 2 | 2 | No |
| Case 3 | 42 | 2 | 1 | No |
| Case 4 | 54 | 3 | 2 | No |

Among the 4 cases associated with VHL, one had a multifocal presentation. One other case showed a locoregional recurrence. Among all the cases, the youngest age of presentation (27 years) was seen in one of the VHL associated case.

## Gross parameters:

### Tumour focality:

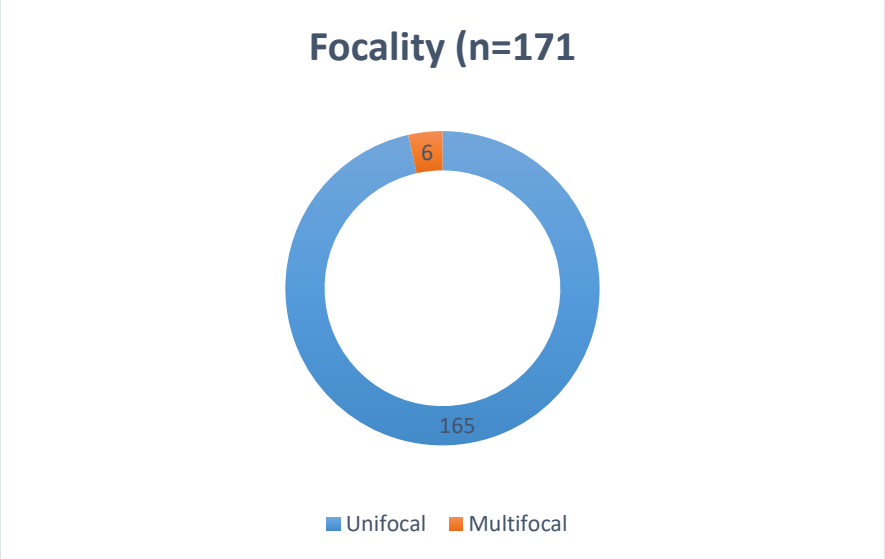



*Figure 14. Distribution of the tumour focality.*

Amongst 171 cases, 96.5% (n=165) of the tumours were unifocal. Multifocal tumours were seen in 3.5% of the cases (n=6). Among the six multifocal cases, one was seen in a VHL associated clear cell renal cell carcinoma.

Syndromic association and focality:

*Table 4. Tumour focality among the VHL associated cases.*

| | Unifocal | Multifocal |
|---|---|---|
| VHL Associated cases (n=4) | 3 | 1 |

One of the four cases (25%) of clear cell renal cell carcinoma which was associated with VHL syndrome was multifocal in presentation.

Type of surgical specimen:

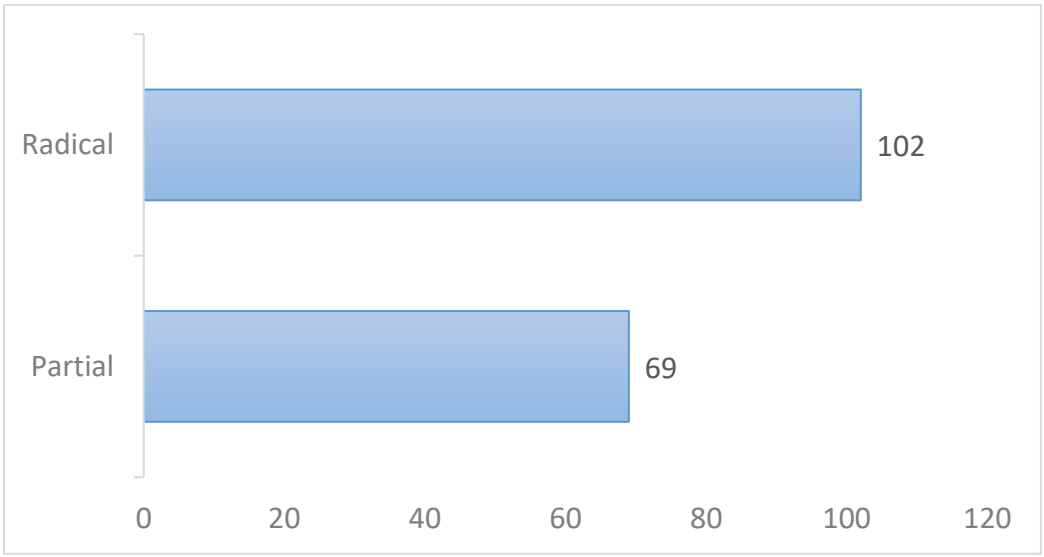



*Figure 15. Distribution of the cases by the surgical procedure.*

Amongst 171 cases, 59.6% of cases (n=102) were specimens of radical nephrectomies while the remaining 40.4% cases (n=69) were nephron sparing partial nephrectomies.

Size of tumour:

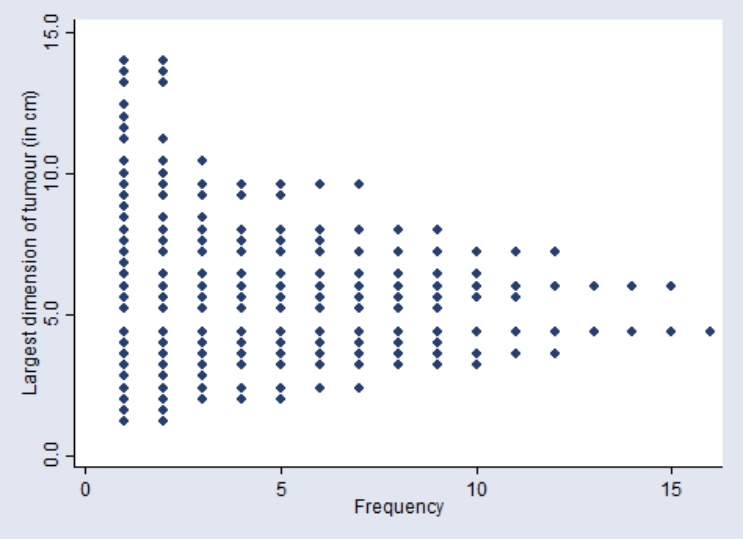



*Figure 16. Distribution of tumours by their size (n=171)*

The mean size of the tumour calculated for all 171 patients was 5.99cm ± 2.81cm with an overall range of 1cm to 14cm.

Hilar lymphadenopathy:

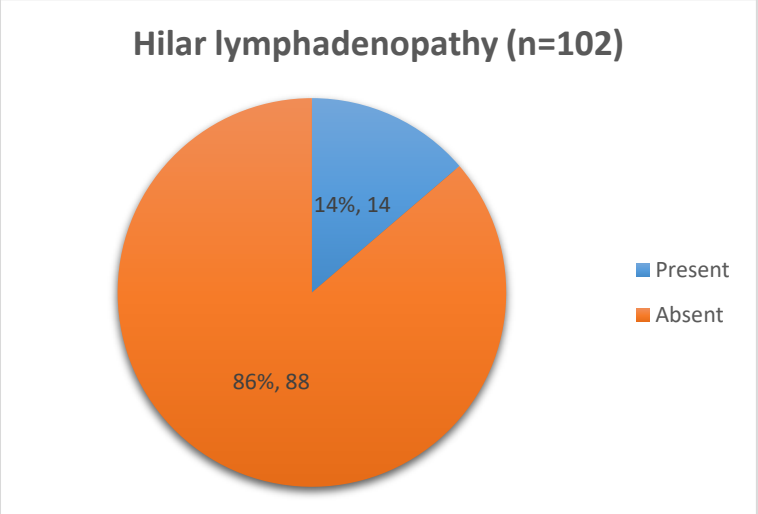



*Figure 17. Distribution of tumours with hilar lymphadenopathy.*

Among the radical nephrectomy cases (n=102), hilar lymphadenopathy was seen on gross examination only in 14% of cases (n=14), of which one case showed chronic lymphocytic leukemia/ small lymphocytic lymphoma involving the lymph node pathologically, but none of them showed metastatic RCC.

**Histological parameters:**

Histological subtype:

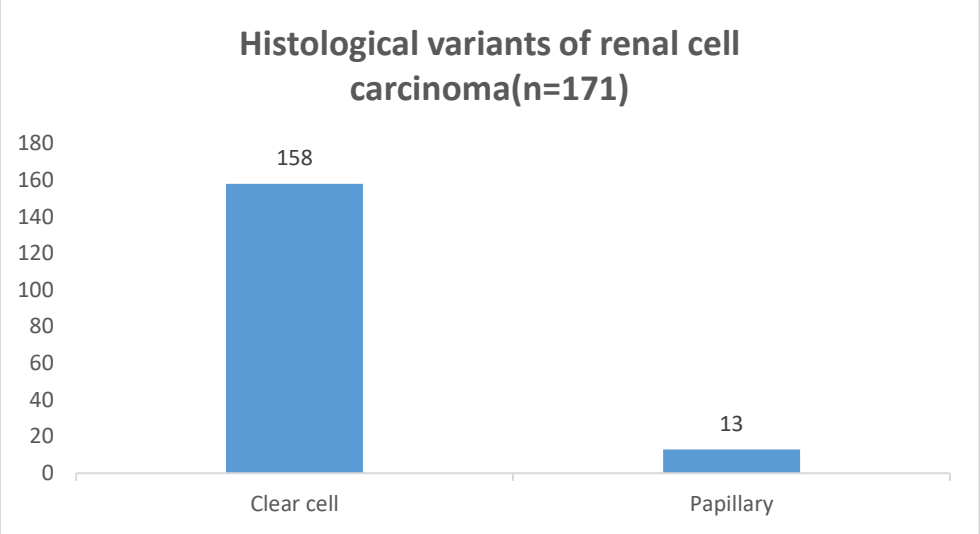



*Figure 18. Distribution of renal cell carcinoma variants.*

Amongst 171 cases, 92.4% (n=158) was of the clear cell variant. The remaining 7.6% (n=13) was papillary carcinoma variant.

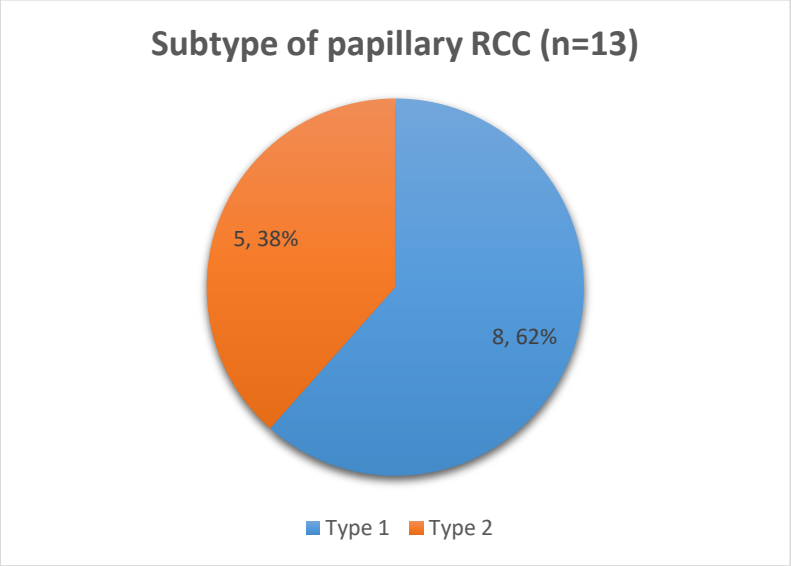



*Figure 19. Subtyping papillary renal cell carcinoma.*

Among the 13 cases of papillary RCC, 61.5% of cases (n=8) showed features of type 1 papillary RCC while the remaining 38.5% of cases (n=5) were type 2 papillary RCC.

*Table 5. Association of different variables with histological subtypes (pRCC vs. ccRCC).*

| Variable | ccRCC | Prcc | p value |
|---|---|---|---|
| **Age** | 52.70 years | 55.15 years | 0.232 |
| **Sex** | | | |
| **Male** | 81.65% | 92.31% | |
| **Female** | 18.35% | 7.69% | 0.331 |
| **Mode of presentation** | | | |
| **Incidental** | 52.53% | 46.15% | |
| **Symptomatic** | 47.47% | 53.85% | 0.658 |
| **Side** | | | |
| **Right** | 53.16% | 61.54% | |
| **Left** | 46.84% | 38.46% | 0.560 |
| **Type of surgery** | | | |
| **Radical nephrectomy** | 60.76% | 46.15% | |
| **Partial nephrectomy** | 39.24% | 53.85% | 0.302 |
| **Fuhrman grade** | | | |
| **Grade 1** | 15.82% | - | |
| **Grade 2** | 55.70% | 61.54% | |
| **Grade 3** | 24.68% | 38.46% | 0.319 |
| **Grade 4** | 3.80% | - | |
| **ISUP grade** | | | |
| **Grade 1** | 51.27% | 30.77% | |
| **Grade 2** | 31.01% | 46.15% | 0.321 |
| **Grade 3** | 12.66% | 23.08% | |
| **Grade 4** | 5.06% | - | |
| **Lymphovascular invasion** | 8.86% | - | 0.263 |
| **Capsular invasion** | 11.39% | 7.69% | 0.683 |
| **Hilar lymphadenopathy** | 8.23% | 7.69% | 0.946 |
| **Tumour necrosis** | 32.91% | 23.08% | 0.466 |

Various clinical and histological parameters between clear cell and papillary renal cell carcinoma were compared but none was statistically significant.

Fuhrman grading:

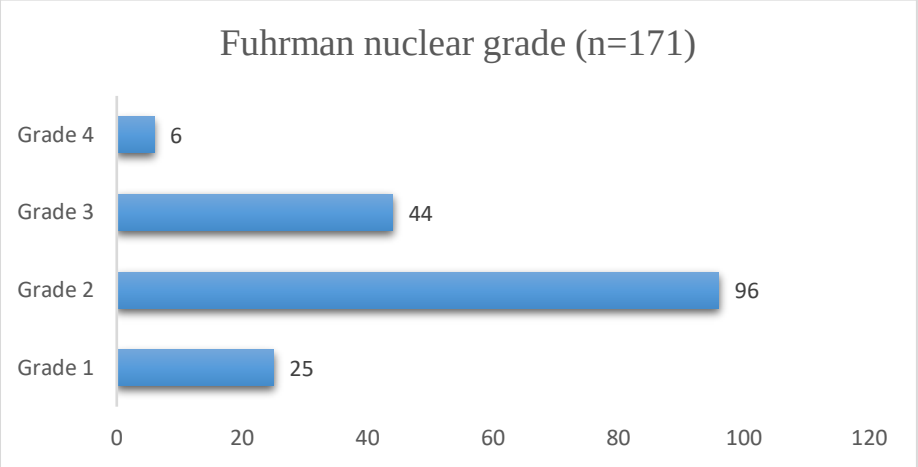



*Figure 20. Distribution of the tumours by the Fuhrman grading system.*

On applying Fuhrman grading for all the 171 cases, there were 14.6% (n=25) cases of Grade 1, 56.1% (n=96) cases of grade 2, 25.7% (n=44) cases of grade 3 and 3.51% (n=6) cases of grade 4 tumours.

ISUP grading system:

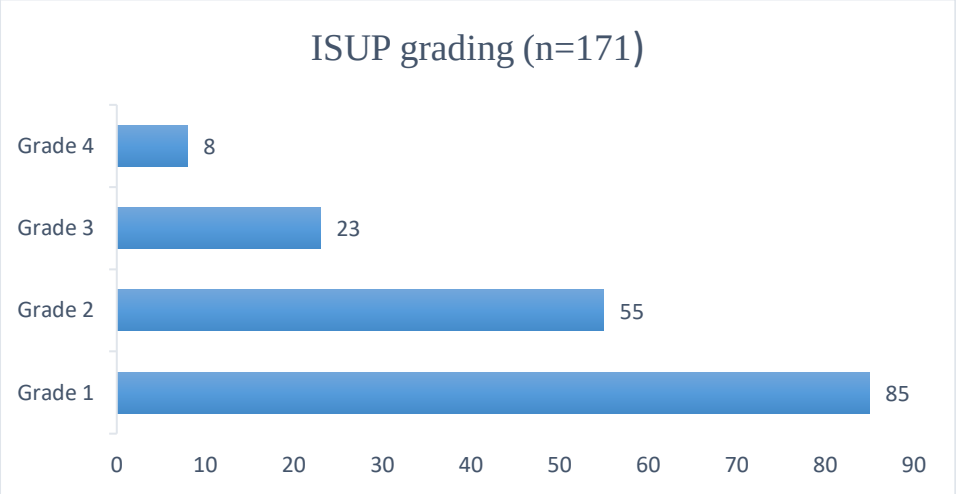



*Figure 21. Distribution of the tumours by the ISUP grading system.*

On applying the ISUP grading system for all the 171 cases showed that, there were 49.7% (n=85) cases of Grade 1, 32.2 % (n=55) cases of grade 2, 13.4% (n=23) cases of grade 3 and 4.7% (n=8) cases of grade 4 tumours.

Fuhrman grading among the subtypes of RCC:

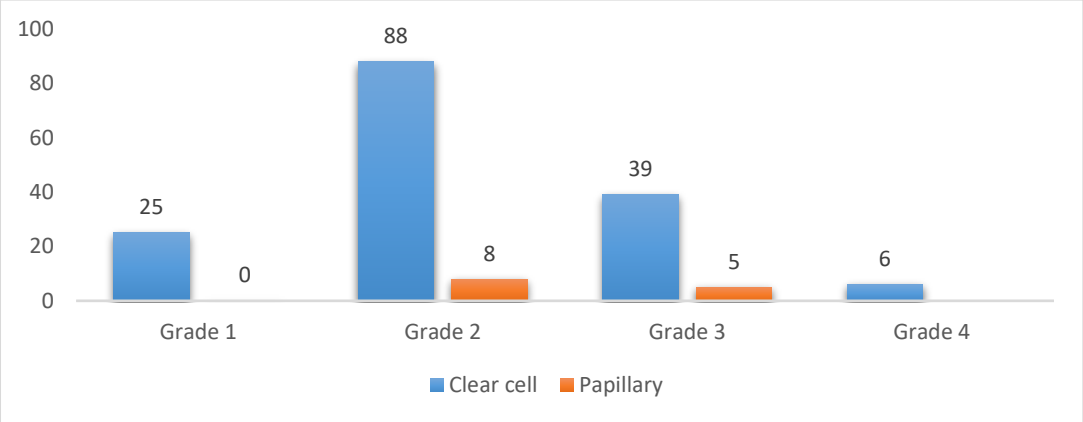



*Figure 22. Fuhrman grading of both ccRCC and pRCC*

On Fuhrman grading, 15.82% ccRCC tumours belonged to grade 1, 55.69% to grade 2, 24.68% and 3.79% cases to grade 3 and grade 4 respectively. There were no grade 1 or grade 4 tumours of papillary renal cell carcinoma.

Subtype of RCC among the ISUP grades:

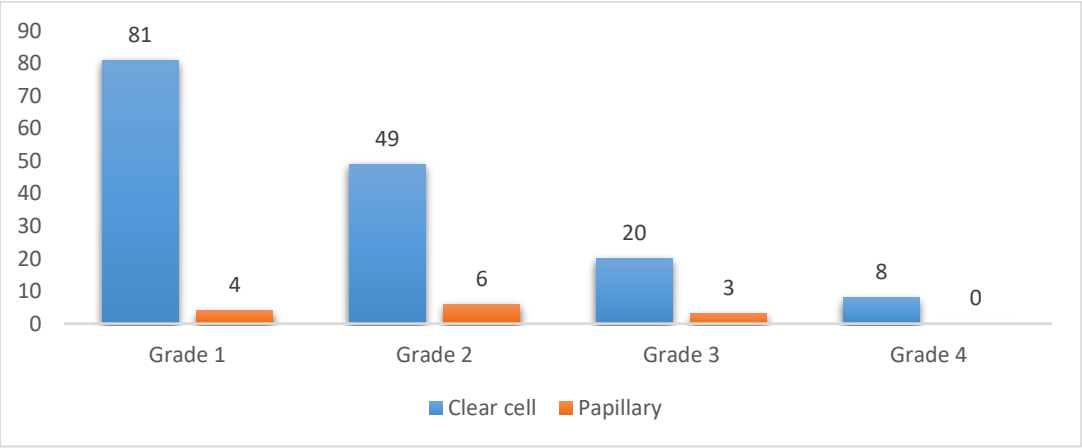



*Figure 23. Grading of both ccRCC and pRCC by ISUP system.*

Applying ISUP grade showed that, up to 51.26% clear cell renal cell carcinomas belonged to grade 1, 31.01% with grade 2, 12.65% with grade 3 and 5.06% with grade 4.

Correlation of nuclear grades with both the systems:

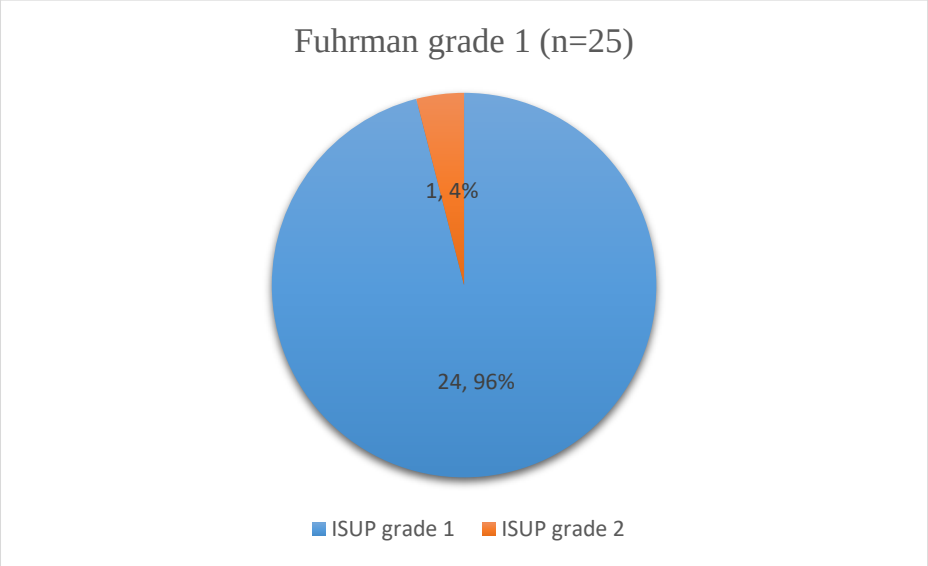



*Figure 24. Fuhrman grade 1 tumours re-graded by ISUP grades.*

Of the 25 cases which were Fuhrman grade 1, 96% of the cases (n=24) continued to be ISUP grade 1 while 1 case was upgraded to ISUP grade 2.

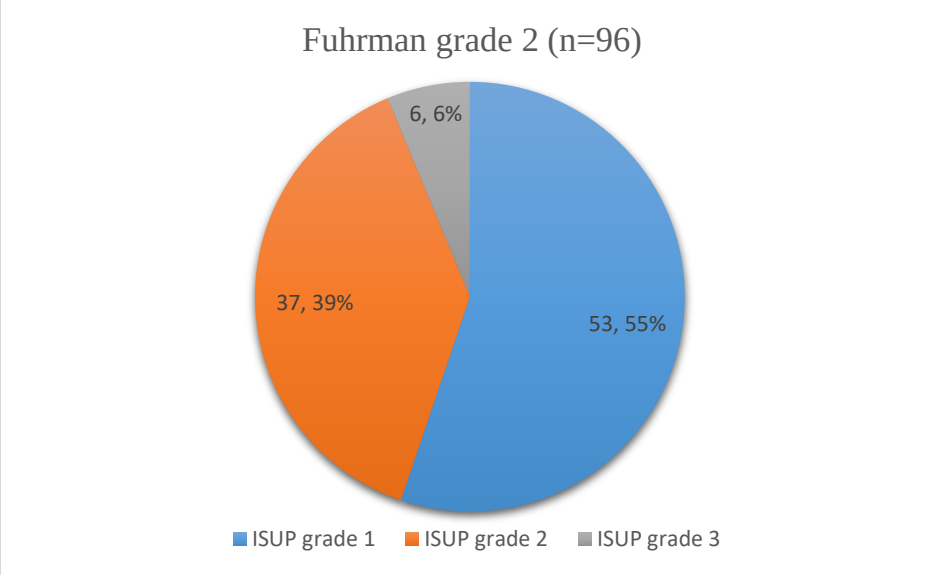



*Figure 25. Fuhrman grade 2 tumours re-graded by ISUP grades.*

Of the 96 cases which were Fuhrman grade 2, 55% of the cases (n=53) were downgraded as ISUP grade 1, 38.5% (n=37) belonged to ISUP grade 2 and 6.5% of cases (n=6) were upgraded to ISUP grade 3.

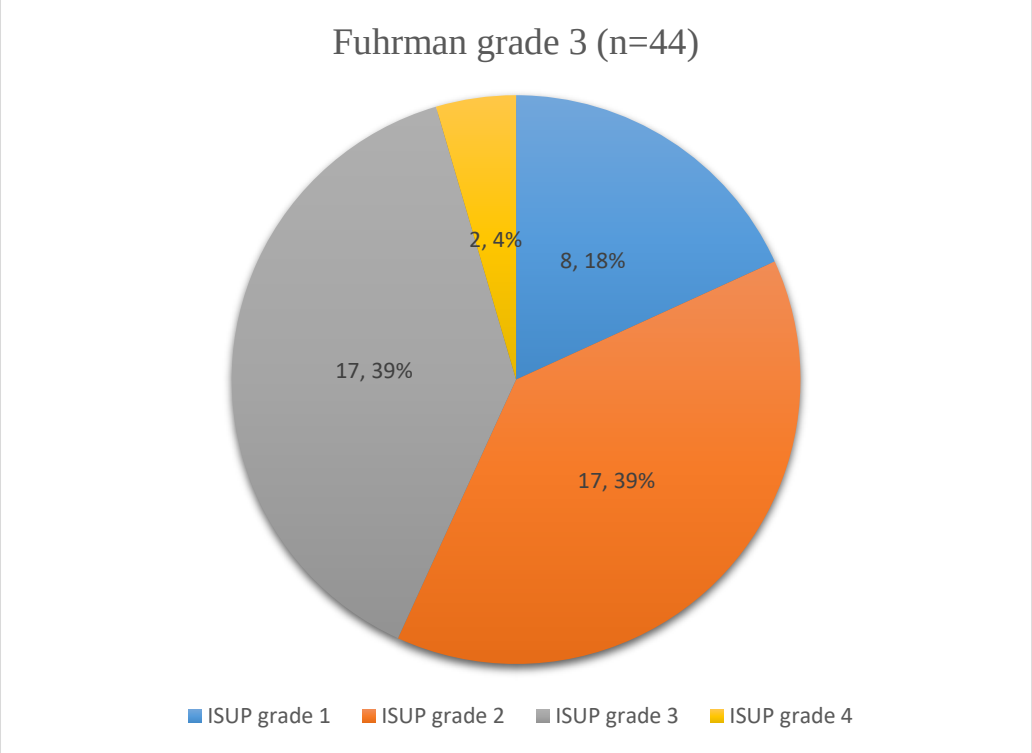



*Figure 26. Fuhrman grade 3 tumours re-graded by ISUP grades.*

Of the 44 cases which were classified as Fuhrman grade 3, 18% of the cases (n=8) were downgraded as ISUP grade 1, 39% (n=17) were downgraded as ISUP grade 2, 39% (n=17) were given as ISUP grade 3 and 4% of cases (n=2) were upgraded to ISUP grade 4.

All 6 cases of Fuhrman grade 4 continued to be of ISUP grade 4.

Age vs Fuhrman grading:

*Table 6. Mean age across the Fuhrman grades.*

| Fuhrman grading | Number of cases | Mean age (Years) |
|---|---|---|
| Grade 1 | 25 | 51.08 |
| Grade 2 | 96 | 51.84 |
| Grade 3 | 44 | 54.70 |
| Grade 4 | 6 | 64.00 |

Comparing the age of the patients with the Fuhrman grading system, showed a significant increase in age with the grade of the tumour (p=0.044).

Age vs ISUP grading:

*Table 7. Mean age across the ISUP grades.*

| ISUP grading | Number of cases | Mean age (Years) |
|---|---|---|
| Grade 1 | 85 | 51.85 |
| Grade 2 | 55 | 52.84 |
| Grade 3 | 23 | 53.09 |
| Grade 4 | 8 | 63.88 |

Comparing the age of the patients with the ISUP grading system, showed an increase in age as the grade increased (p=0.476).

| ISUP system | Grade 1 | Grade 2 | Grade 3 |
|---|---|---|---|
| Grade 1 | - | 1 | - |
| Grade 2 | 1 | - | - |
| Grade 3 | 1 | 1 | - |
| Grade 4 | 0.029* | 0.068 | 0.133 |

*Table 8. Comparing p-value between ISUP grades for age*

Comparing between age and the various ISUP grades showed statistical significance between age of presentation in ISUP grade1 with grade 4 (p=0.0029) but not between other grades.

## Size of tumour vs nuclear grade:

Size vs Fuhrman grade:

*Table 9. Mean size of tumour in Fuhrman grades*

| Fuhrman Grade | Mean size ( in cm) |
|---|---|
| Grade 1 | 4.45 |
| Grade 2 | 5.82 |
| Grade 3 | 6.75 |
| Grade 4 | 9.50 |

Size vs ISUP grade:

*Table 10. Mean size of tumour in ISUP grades*

| ISUP Grade | Mean size ( in cm) |
|---|---|
| Grade 1 | 5.37 |
| Grade 2 | 6.49 |
| Grade 3 | 5.58 |
| Grade 4 | 10.25 |

The size of the tumours increased with grades according to both Fuhrman and ISUP system. Fuhrman grade 1 tumours showed a mean size of 4.45cm while in grade 4 it was 9.50cm. ISUP grade 1 tumours showed a mean of 5.37cm while in ISUP grade 4 it was 10.25cm.

*Table 11. Comparing size of tumour with ISUP grades*

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Grade 1 | 1 | 0.138 | 0.004* | 0.001* |
| Grade 2 | - | 1 | 0.340 | 0.007* |
| Grade 3 | - | - | 1 | 0.113 |

Comparing size of the tumour with ISUP grades showed statistical significance between the sizes of grade 1 compared with grade 3 and grade 4 tumours and grade 2 tumours compared with grade 4 tumours respectively.

Other statistically significant histological parameters compared with the grading systems:

*Table 12.Comparing histological parameters between the grading systems.*

| | Fuhrman grades 1-4 | ISUP grades 1-4 |
|---|---|---|
| Lymphovascular invasion | p=0.008* | p=0.222 |
| Renal sinus invasion | p=0.079 | p=0.079 |
| Capsular invasion | p=0.001* | p=0.004* |
| Tumour necrosis | p<0.001* | p<0.001* |

Comparing histological parameters within Fuhrman and ISUP grading systems showed that there was statistical significance between the Fuhrman grades with regard to lymphovascular invasion(p=0.008), capsular invasion (p=0.001) and tumour necrosis (p<0.001) whereas with ISUP grades, capsular invasion (p=0.004) and Tumour necrosis (p<0.001) were the only significant parameters.

Hilar lymphadenopathy vs ISUP grading system:

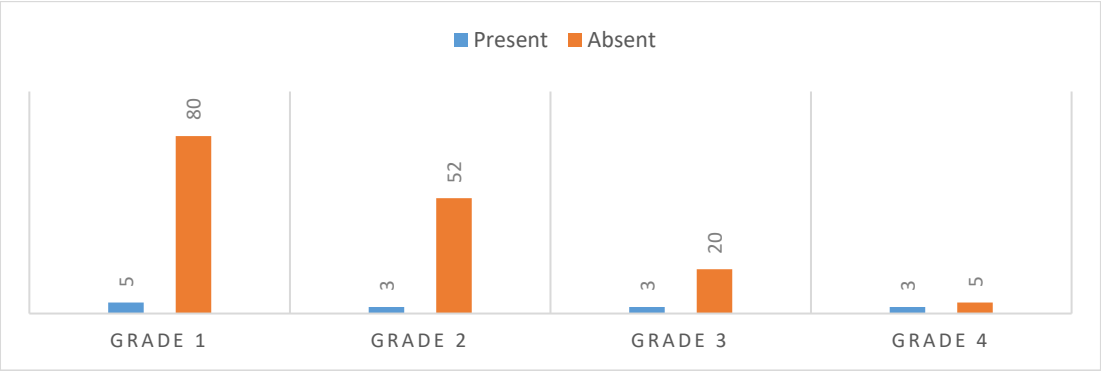



*Figure 27. Hilar lymphadenopathy in ISUP grades*

Hilar lymphadenopathy was seen highest in ISUP grade 4 tumours, which was statistically significant. (p= 0.012). It was seen in 38% of ISUP grade 4 tumours compared to 6% of ISUP grade 1 tumours.

Capsular invasion:

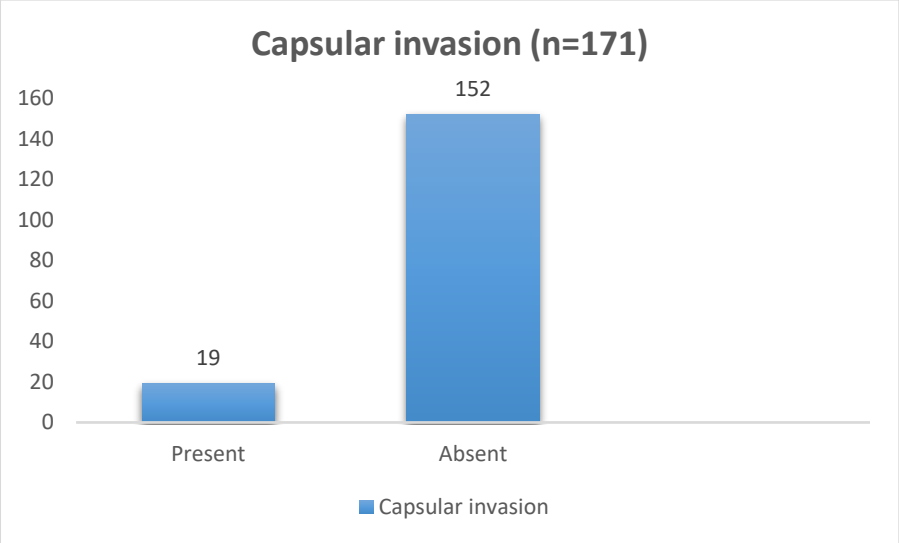



*Figure 28. Capsular invasion in tumours*

Among 171 cases, capsular invasion was seen 11.11% (n=19) of the cases.

Perinephric fat invasion:

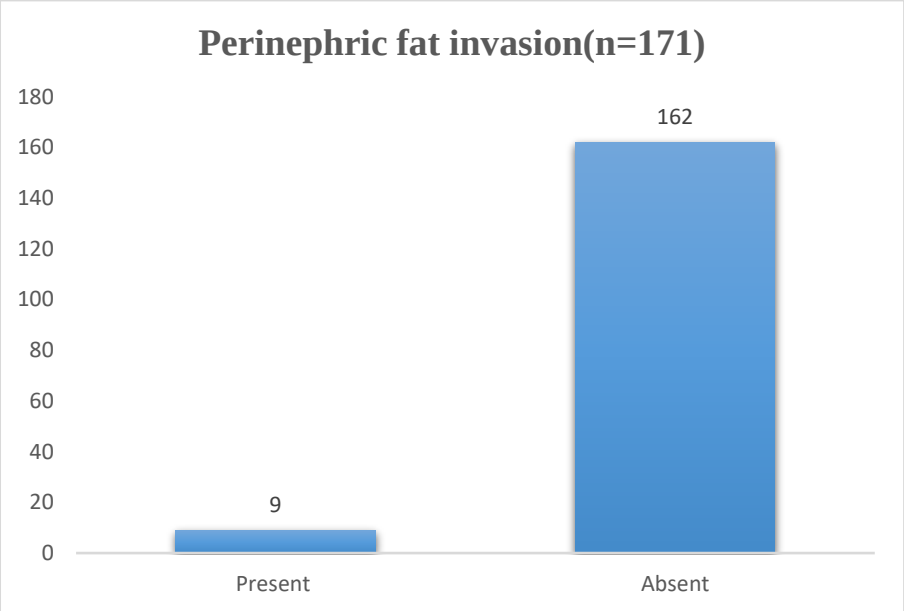



*Figure 29. Perinephric fat invasion in tumours*

Among 171 cases, perinephric fat invasion was seen 5.26% (n=9) of the cases.

Sinus fat invasion:

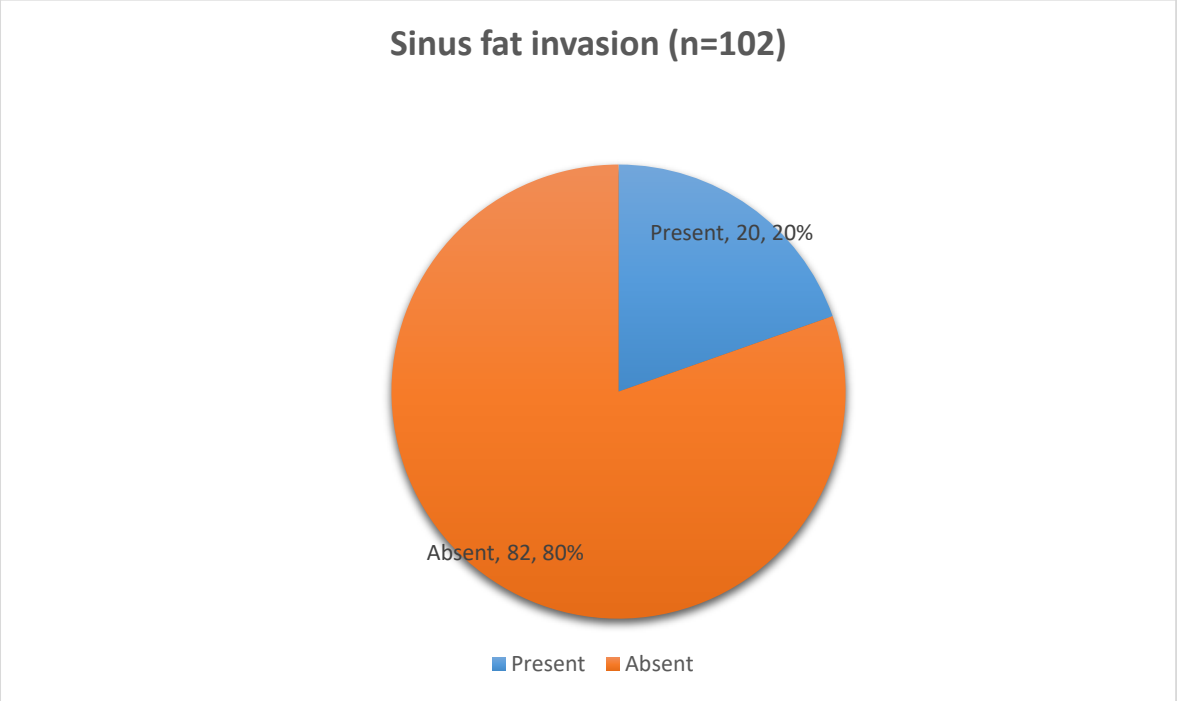



*Figure 30. Sinus fat invasion in tumours*

Renal pelvis invasion:

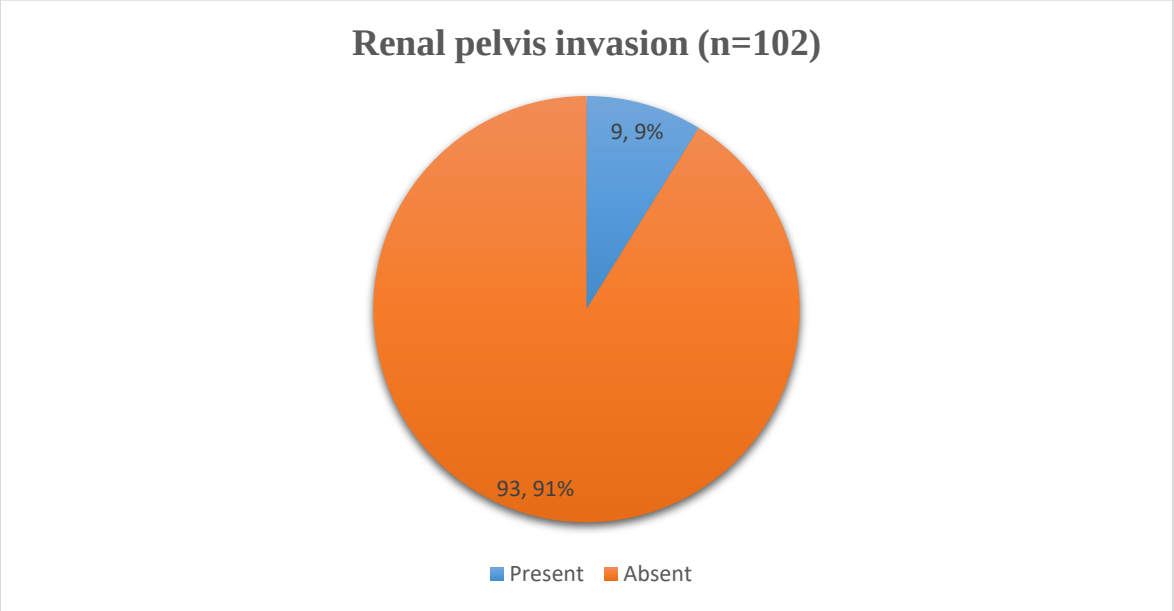



*Figure 31. Renal pelvis invasion in tumours*

20 of 102 cases (20%) showed sinus fat invasion and renal pelvis invasion was seen in 9 of 102 cases (9%).

Lympho-vascular invasion:

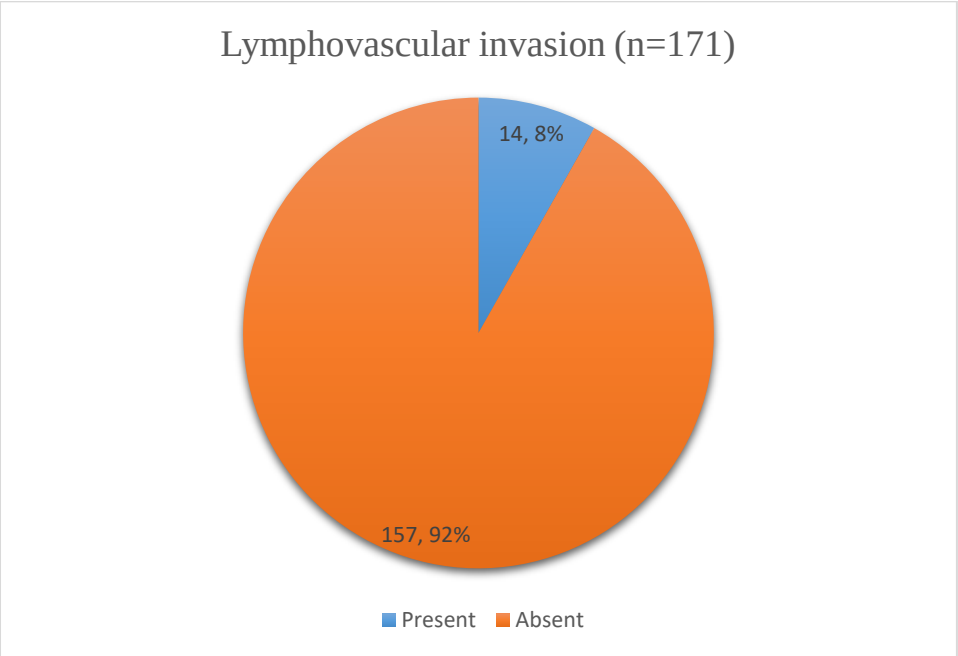



*Figure 32. Lymphovascular invasion in tumours*

Among 171 cases, lymphovascular invasion was seen in 8.18% (n=14) of the cases.

Tumour necrosis:

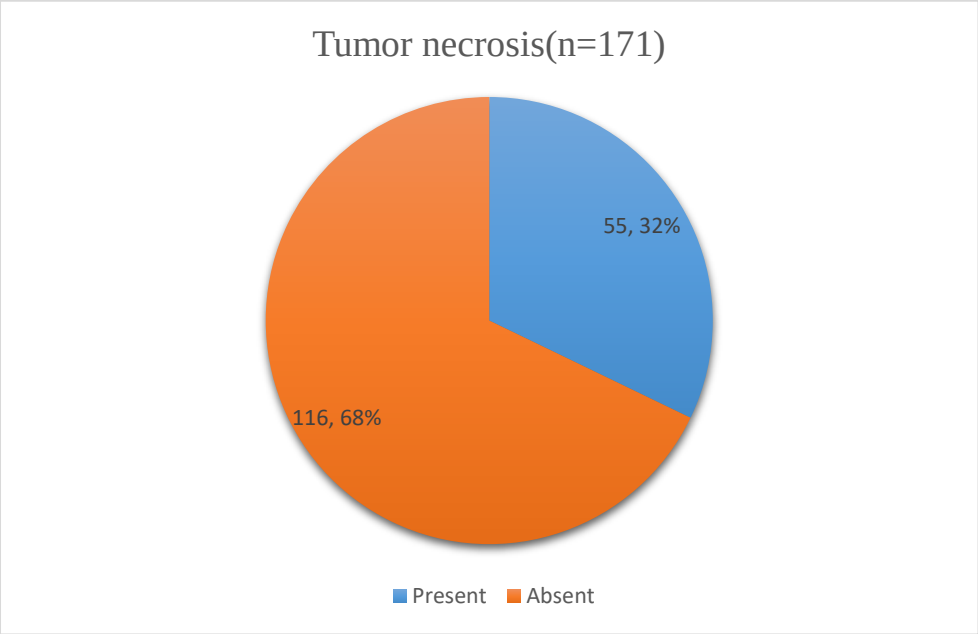



*Figure 33. Tumour necrosis in tumours*

Among 171 cases, tumour necrosis was seen in 32.16% (n=55) of the cases.

Necrosis vs Tumour size:

*Table 13. Tumour necrosis and the mean size of tumour*

| Necrosis | Mean size of tumour (in Cm) |
|---|---|
| Present (n=55) | 7.49 |
| Absent (n=116) | 5.28 |

Tumour necrosis was seen in 55 of the 171 cases and the mean tumour size of those cases was 7.49cm.

Tumour thrombus:

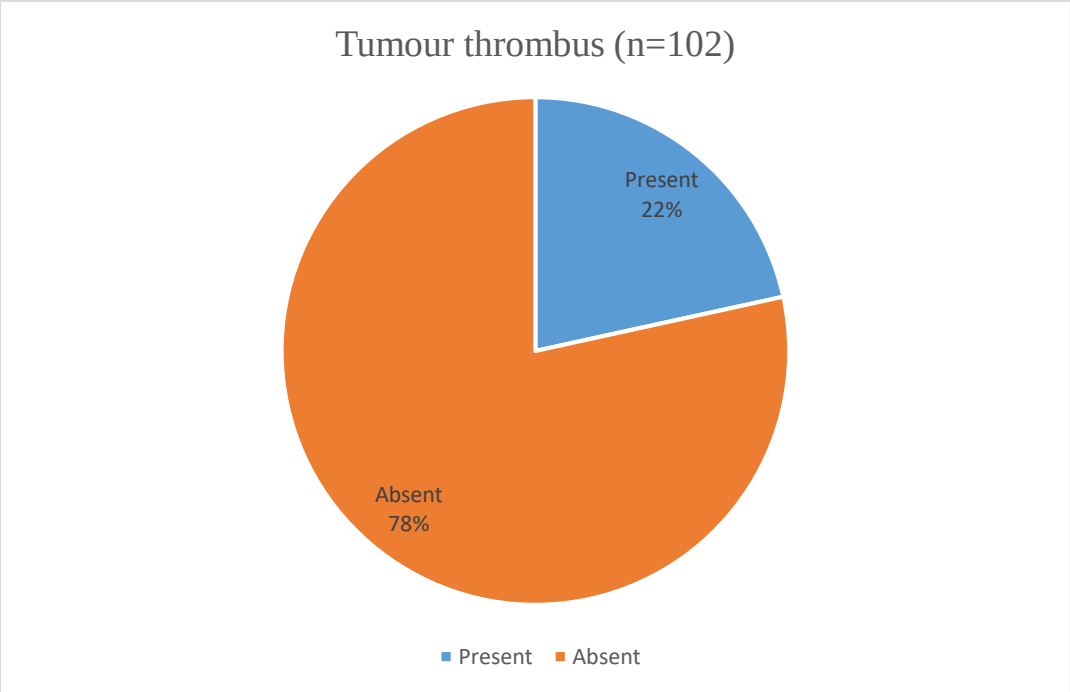



*Figure 34. Tumour thrombus among renal tumours*

Among 102 cases, tumour thrombus was seen in 22% (n=22) of the cases.

Pathological stage:

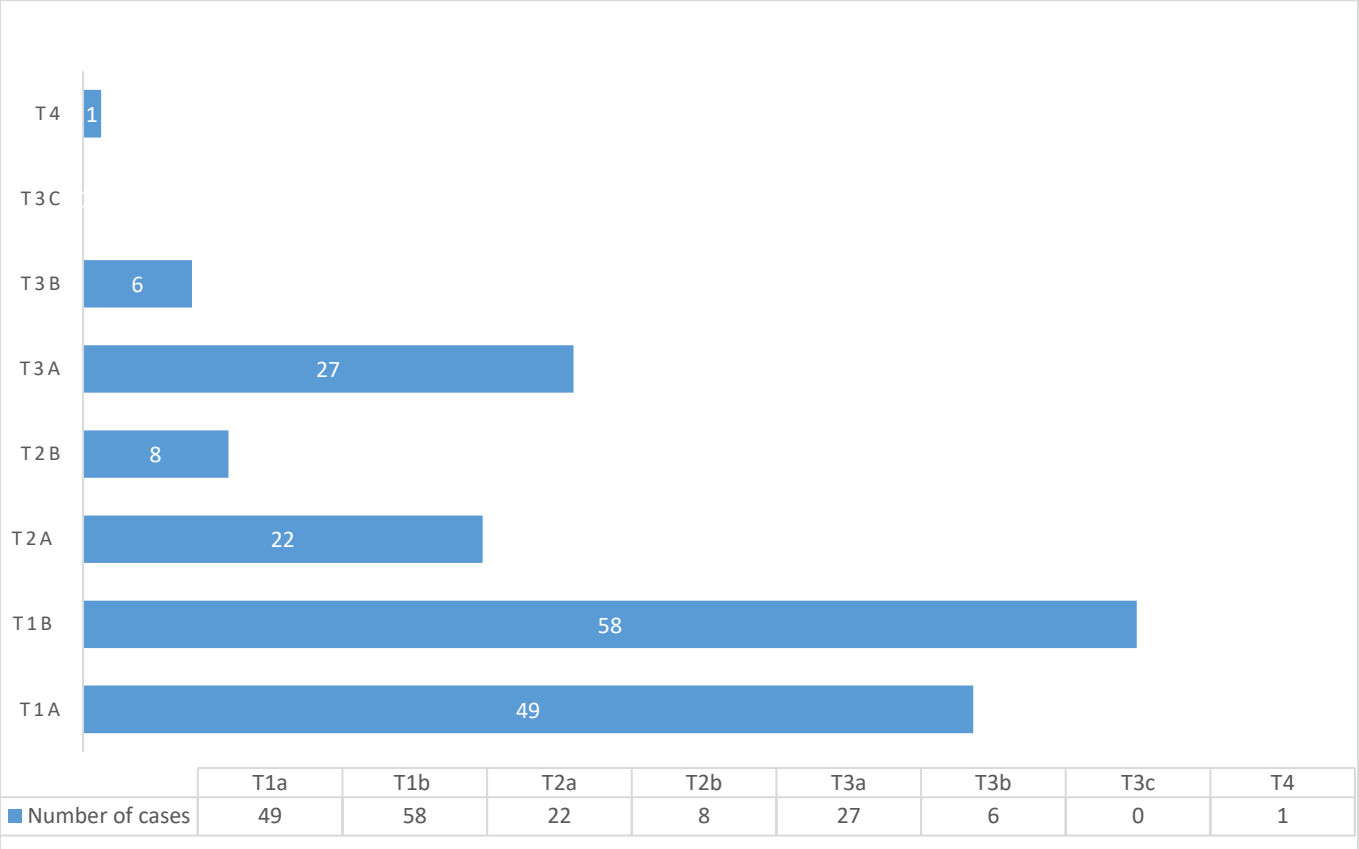
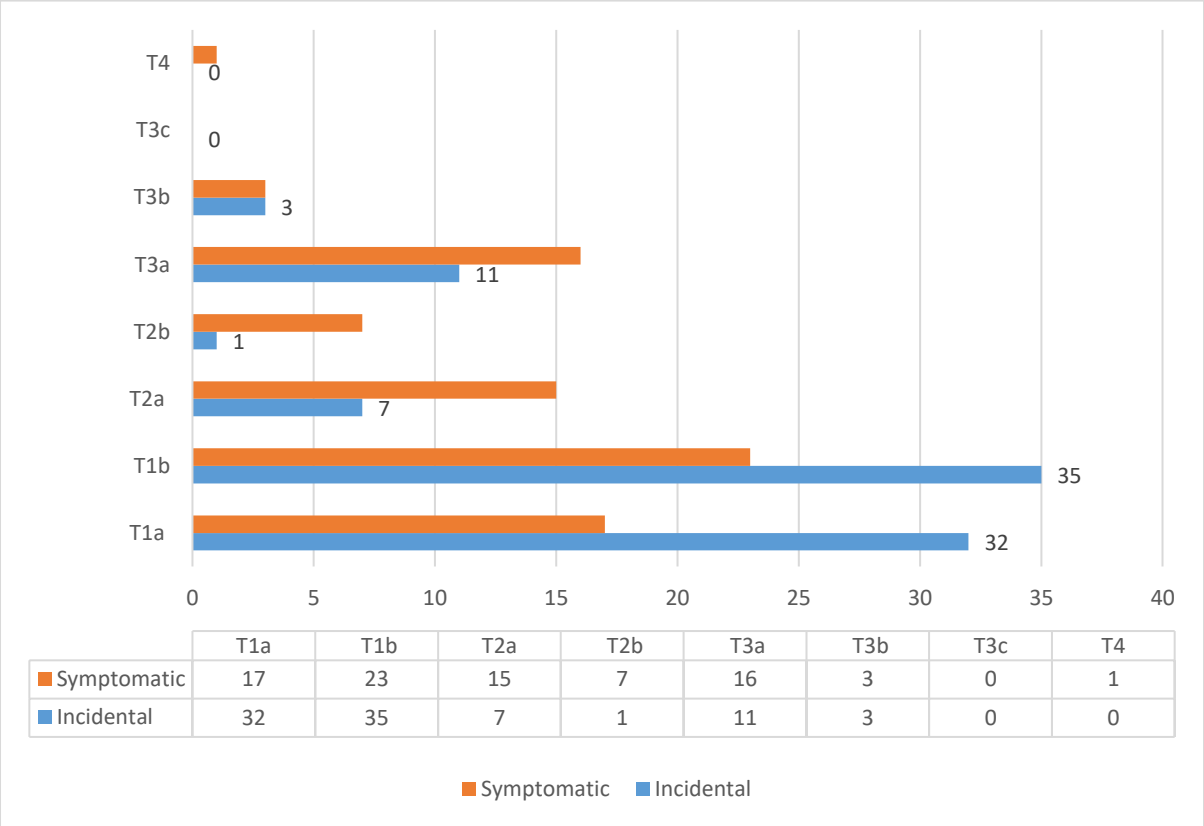



*Figure 35. Pathological staging of the tumours*

Pathological staging for all the 171 tumour cases showed that there were 28% cases (n=49) with T1a stage, 33.9% cases (n=58) with T1b stage, 12.9% cases (n=22) with T2a stage, 4.7% cases (n=8) with T2b stage, 15.79% cases (n=27) with T3a stage, 3.5% cases (n=6) with T3b stage and 0.6% cases (n=1) with T4 stage. There were no cases with T3c staging.

Pathological stage among incidental tumours:




| | T1a | T1b | T2a | T2b | T3a | T3b | T3c | T4 |
|---|---|---|---|---|---|---|---|---|
| Symptomatic | 17 | 23 | 15 | 7 | 16 | 3 | 0 | 1 |
| Incidental | 32 | 35 | 7 | 1 | 11 | 3 | 0 | 0 |

*Figure 36. Pathological staging among the incidentally detected tumours.*

Pathological staging showed that there were 49 cases of pT1a stage and 58 cases of pT1b stage of which 65% of pT1a tumours (32/49) and 62% of pT1b tumours (35/58) were incidentally detected. 27% of pT2 tumours were incidentally detected. 14/33 pT3 tumours were incidentally detected and none in pT4.

Comparing both the grading systems with pathological staging:

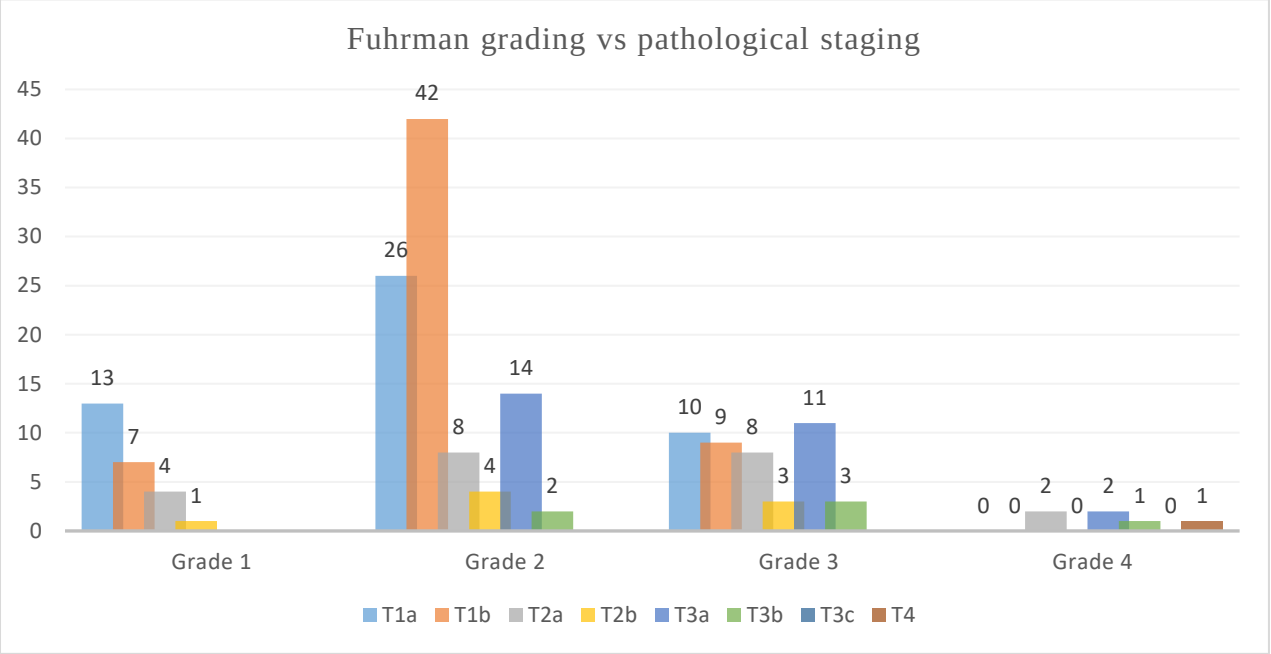



*Figure 37. Fuhrman grade correlated with pathological stages.*

80% of stage I tumours showed Fuhrman grade 1 and none of stage 3 or 4 cases had Fuhrman grade 1.

70.83% of total Fuhrman grade 2 tumours show stage 1 disease while 12.5% with stage 2 disease and 16.66% cases with stage 3 disease.

32% of the total Fuhrman grade 3 tumours belonged to stage 3 and 67% of Fuhrman grade 4 tumours to combined stage 3 and 4.

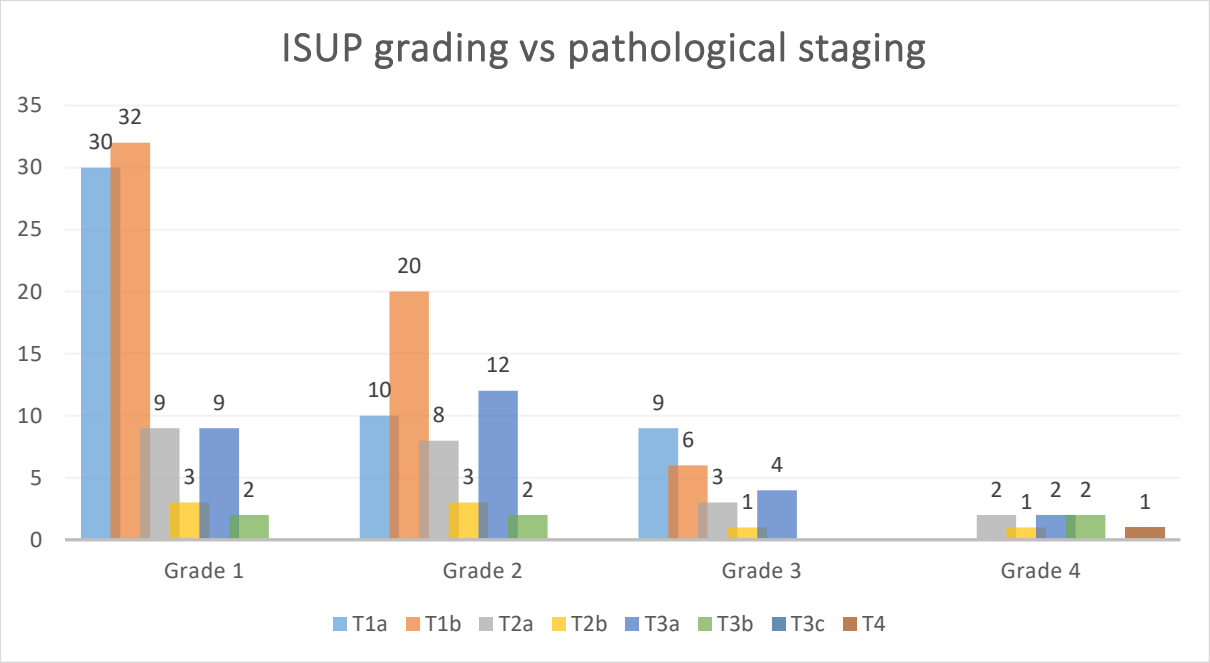



*Figure 38. ISUP grade correlated with pathological stages.*

Of the 85 cases in ISUP grade 1, 73% were stage 1 disease, 14% were stage 2 disease and 13% were stage 3 disease.

There were a total of 55 cases of ISUP grade 2 tumours of which 54.5% were of stage 1 disease, 20% were stage 2 disease and 24.5% were of stage 3 disease.

There were 23 cases of ISUP grade 3 of which 65% (n=15) were stage 1 disease, while Stage 2 and stage 3 diseases were 17.39% cases each.

## Follow up:

The follow up duration ranged from a minimum of 12 months to 5 years and 6 months with a mean of 2 years and 7 months. On follow up of the patients, 18 of them showed metastasis of which 5 also showed locoregional recurrence of the disease.

## Disease free survival:

153 out of the 171 patients were free of disease at the time of their last follow up. The mean disease free survival was 4 years 11 months with an overall range of 4 years 8 months to 5 years 2 months.

## Univariate analysis:

An event was defined as metastasis or recurrence of the tumour. This was detected mainly by sensitive radiological investigations (PET scan) and biopsy proven in a few cases. However both were taken into account for survival analysis.

*Table 14. EFS for clinical parameters in renal cell carcinoma*

| Clinical parameters | | Mean survival (in months) | Events | 95%C.I | P value |
|---|---|---|---|---|---|
| Sex | Male | 59.2 | 15 | 56.1 - 62.3 | 0.79 |
| | Female | 48.3 | 3 | 45.4 - 51.2 | |
| Presentation | Incidental | 62.7 | 4 | 59.6 - 65.7 | 0.011* |
| | Symptomatic | 53.9 | 14 | 49.6 - 57.9 | |
| Comorbidities | DM | 52.5 | 3 | 41.8 - 63.2 | |
| | HT | 56.9 | 5 | 52.7 - 61.1 | 0.10 |
| | DM & HT | 64 | 1 | 60.2 - 67.8 | |
| Side of tumour | Right | 59.4 | 10 | 55.7 - 63.1 | 0.80 |
| | Left | 56.7 | 8 | 53.2 - 60.1 | |
| Syndromic Association | Yes | 42 | 1 | 32.3- 51.7 | 0.29 |
| | No | 59.5 | 17 | 56.7 - 62.3 | |
| Surgical procedure | Partial | 57.9 | 5 | 54.6 - 61.2 | 0.31 |
| | Radical | 58.3 | 13 | 54.5 - 62.00 | |

On comparing various demographic and clinical parameters it was found that event free survival in patients with incidental versus symptomatic presentation was significant with a p value of 0.011.

*Table 15. EFS for histological parameters in renal cell carcinoma*

| Histological parameters | | Mean survival (in months) | Events | 95%C.I | P value |
|---|---|---|---|---|---|
| Histological type | Clear cell | 59.11 | 17 | 56.1 - 62.1 | 0.70 |
| | Papillary | 57.7 | 1 | 49.9 - 65.4 | |
| Fuhrman grade | Grade 1 | 53 | 0 | 53 – 53 | 0.008* |
| | Grade 2 | 58.1 | 8 | 55.0 - 61.2 | |
| | Grade 3 | 54.9 | 8 | 48.2 - 61.6 | |
| | Grade 4 | 37.5 | 2 | 27.6 - 47.4 | |
| ISUP grade | Grade 1 | 62.3 | 5 | 59.2 - 65.4 | 0.0303* |
| | Grade 2 | 53.3 | 8 | 48.8 - 57.9 | |
| | Grade 3 | 57.5 | 2 | 49.3 - 65.6 | |
| | Grade 4 | 44 | 3 | 31.9 - 56.1 | |
| Sinus fat invasion | Present | 56.7 | 4 | 48.6 - 64.8 | 0.42 |
| | Absent | 58.1 | 14 | 55.3 - 60.9 | |
| Lympho-vascular Invasion | Present | 39.5 | 5 | 26.4 - 52.6 | <0.001* |
| | Absent | 60.6 | 13 | 57.9 - 63.3 | |
| Capsular invasion | Present | 54.1 | 5 | 44.8 - 63.3 | 0.08 |
| | Absent | 58.8 | 13 | 56.1 - 61.4 | |
| Tumour Necrosis | Present | 57.2 | 7 | 52.6 - 61.9 | 0.75 |
| | Absent | 59.6 | 11 | 56.1 - 63.1 | |

Event free survival among the various histological parameters showed statistical significance in Fuhrman nuclear grading ($p=0.008$), ISUP grading system ($p=0.03$) and lympho-vascular invasion ($p<0.001$).

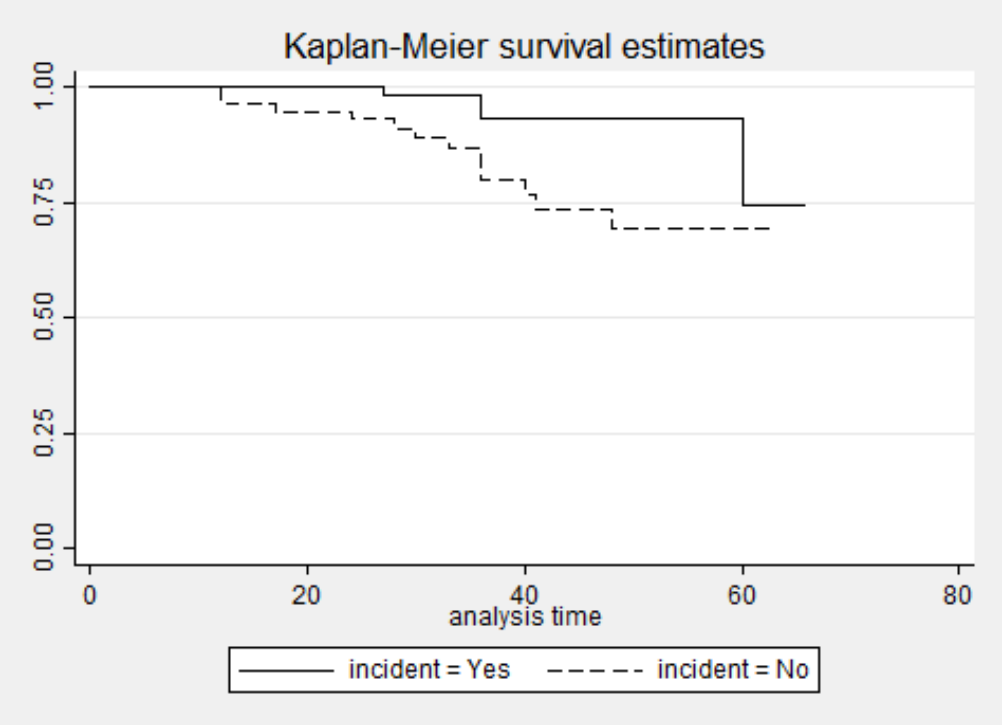



*Figure 39. EFS vs Clinical presentation (p=0.01)*

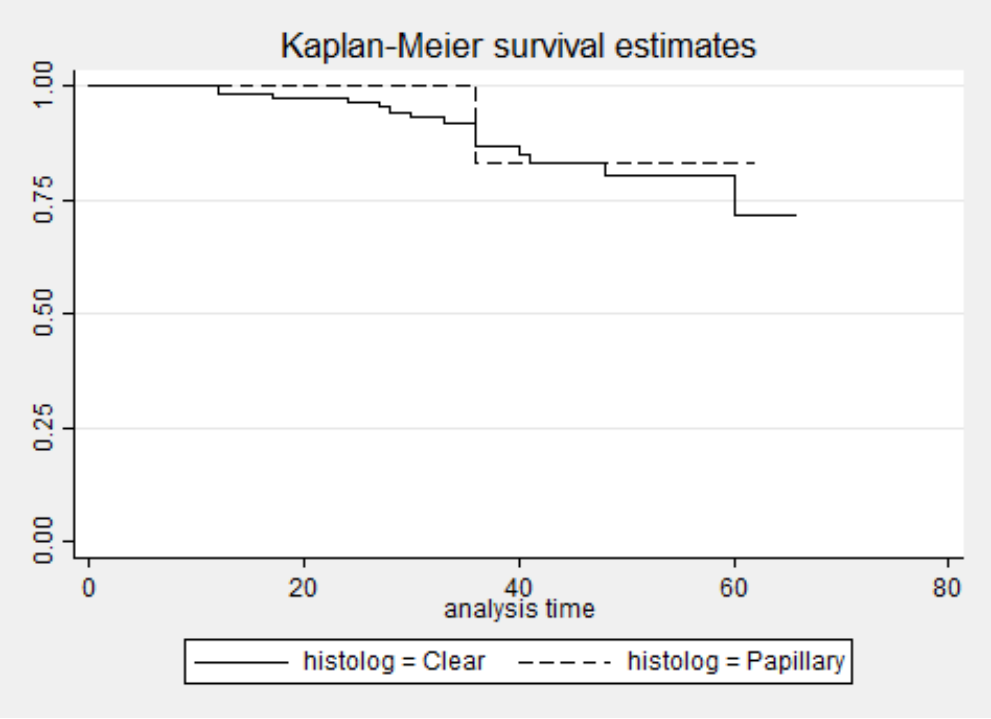



*Figure 40. EFS vs histological subtype (p=0.70)*

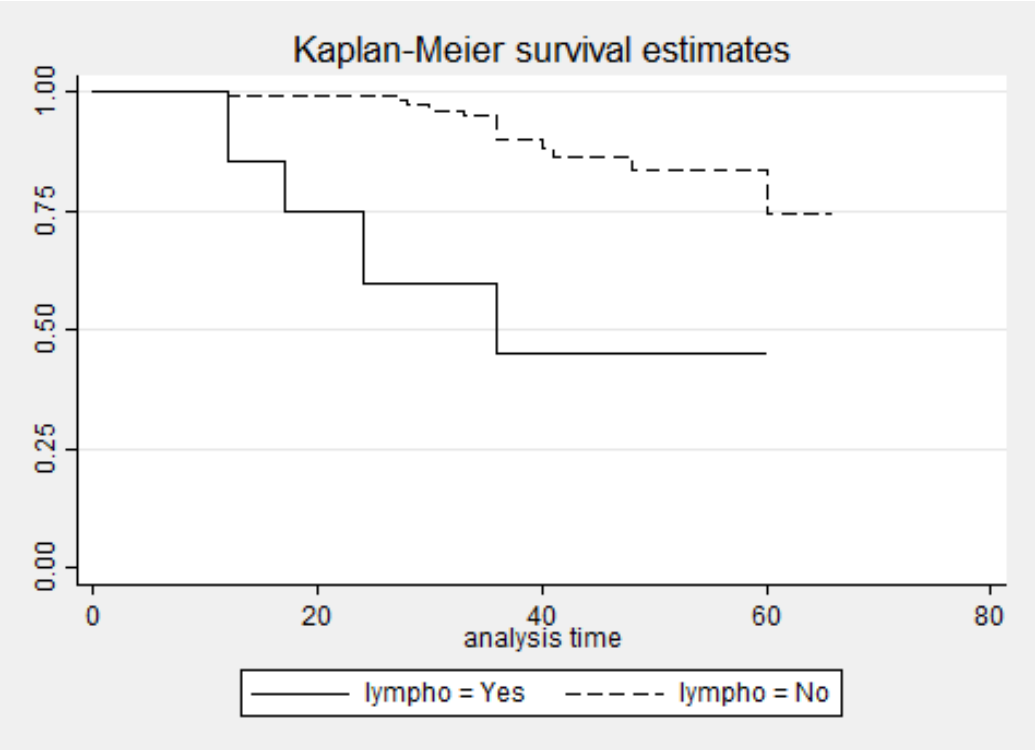



*Figure 41. EFS vs Lymphovascular invasion (p<0.001)*

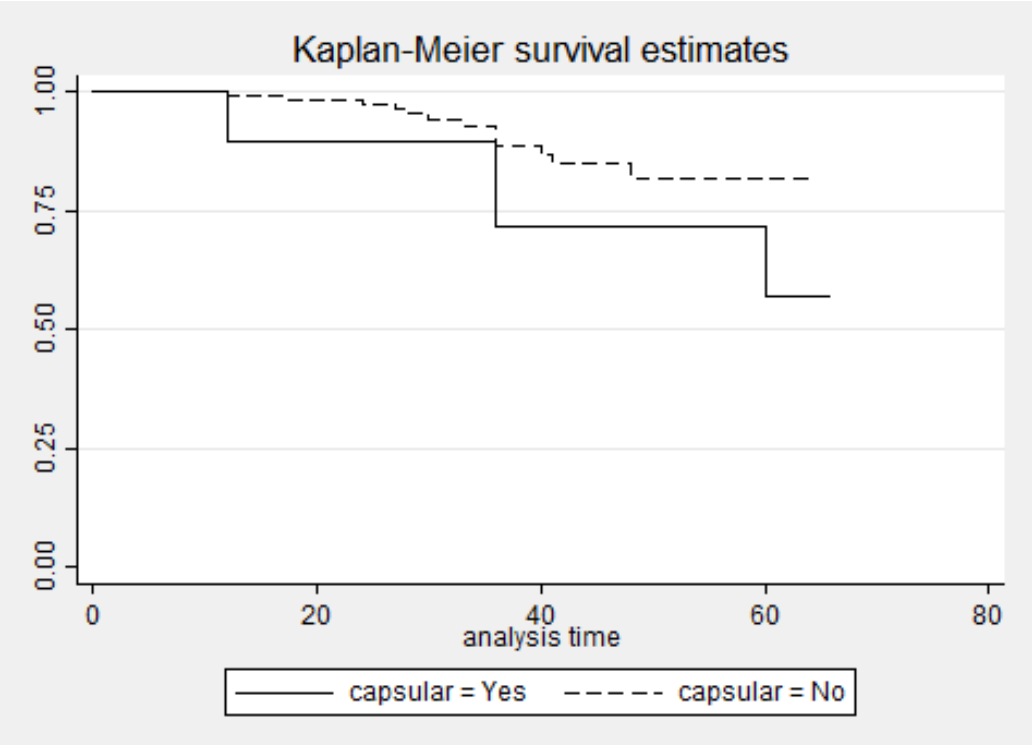



*Figure 42. EFS vs Capsular invasion (p=0.08)*

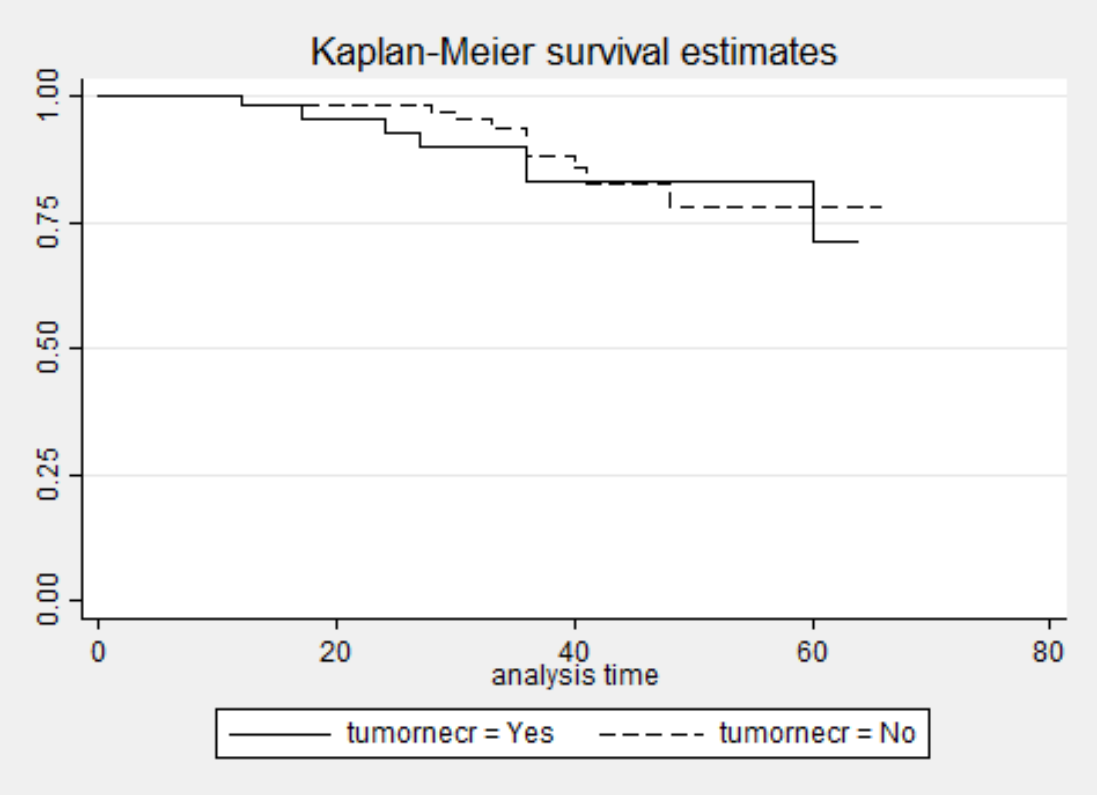



*Figure 43. EFS vs tumour necrosis (p=0.75)*

*Table 16. EFS in the Fuhrman grades*

| Fuhrman grade | Number of cases | Mean survival (in months) | 95% CI |
|---|---|---|---|
| **Grade 1** | 25 | 53 | 53-53 |
| **Grade 2** | 96 | 58.12 | 55.04 - 61.21 |
| **Grade 3** | 44 | 54.92 | 48.23 - 61.62 |
| **Grade 4** | 6 | 37.5 | 27.63 - 47.36 |

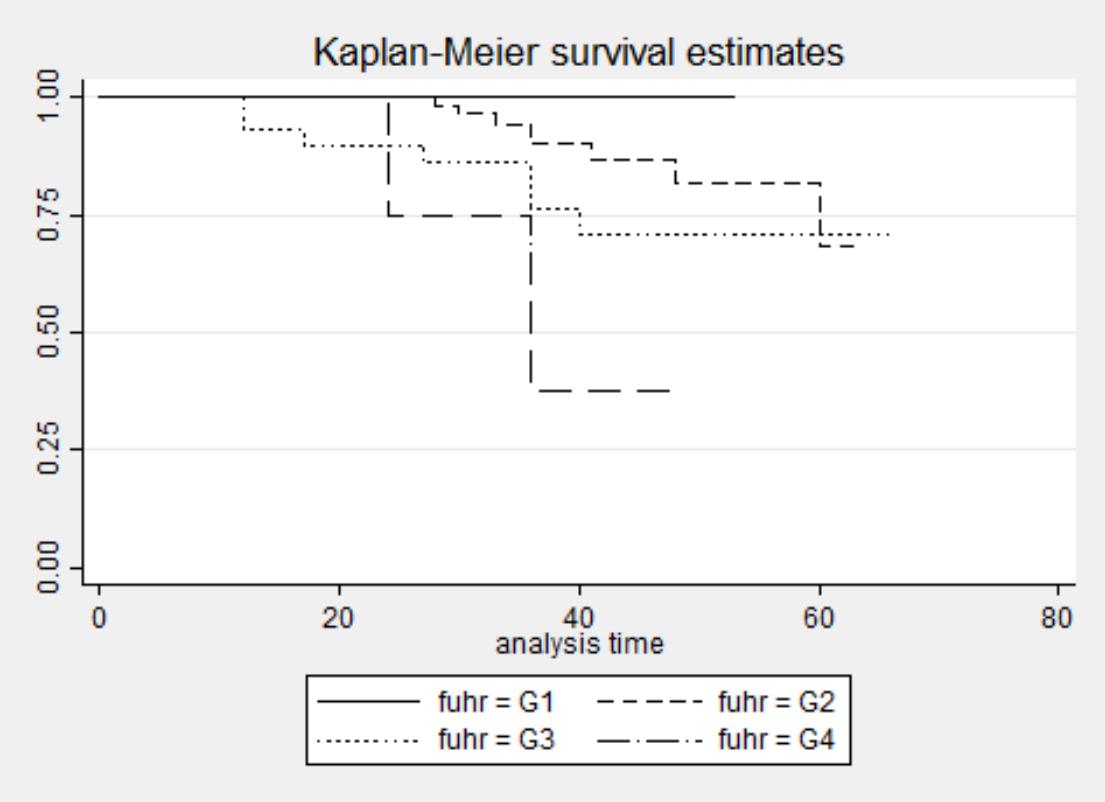



*Figure 44. EFS vs Fuhrman grading (p=0.008)*

*Table 17.EFS in the ISUP grades*

| ISUP grade | Number of cases | Mean survival(in months) | 95%CI |
|---|---|---|---|
| **Grade 1** | 85 | 62.29 | 59.21 - 65.38 |
| **Grade 2** | 55 | 53.29 | 48.77 - 57.82 |
| **Grade 3** | 23 | 57.45 | 49.30 - 65.60 |
| **Grade 4** | 8 | 44 | 31.86 - 56.13 |

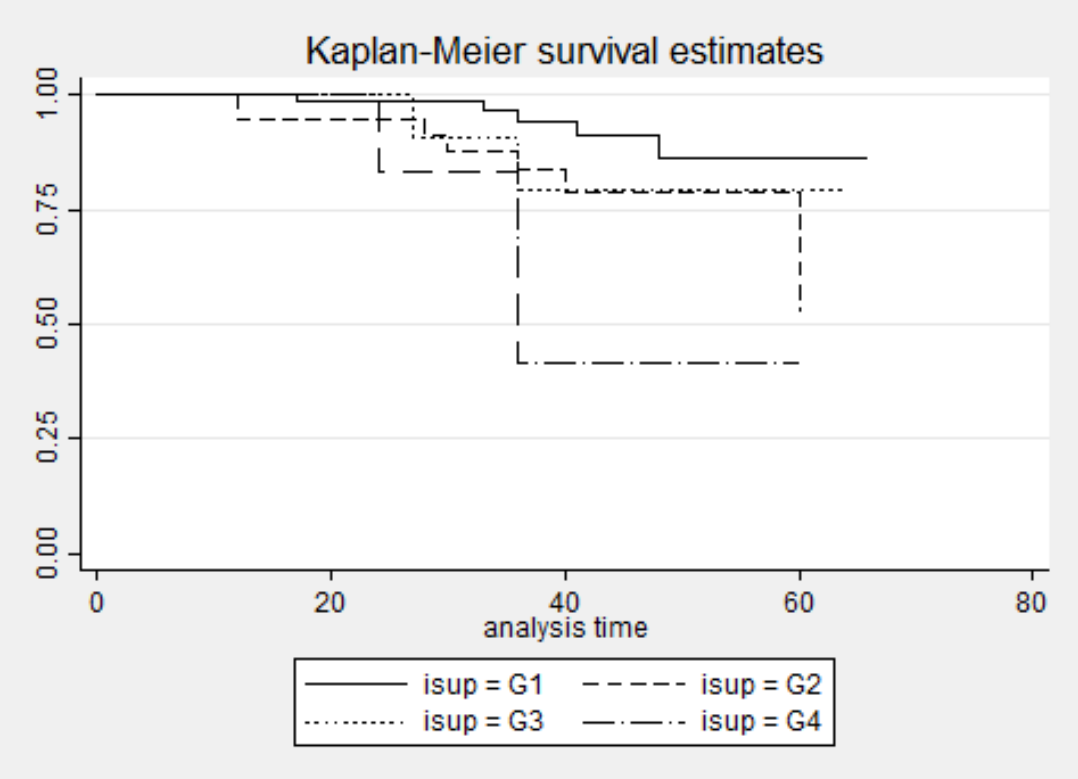



*Figure 45. EFS vs ISUP grading (p=0.03)*

Multivariate analysis:

To evaluate the independent factors of prognostic significance, multivariate analysis was done and hazard ratios were calculated.

*Table 18. Multivariate analysis of event free survival*

| Variables | HR | 95% CI | p value |
|---|---|---|---|
| **Symptomatic at presentation** | 3.188 | 1.0 - 10.10 | 0.049* |
| **Capsular invasion** | 1.15 | 0.31 - 4.32 | 0.827 |
| **Lympho-vascular invasion** | 3.895 | 1.11 - 13.60 | 0.033* |
| **Fuhrman system** | 1.877 | 0.73 - 4.77 | 0.186 |
| **ISUP grading** | 1.073 | 0.56 - 2.04697 | 0.829 |

On multivariate analysis, the factors that were found to have independent prognostic significance were the symptoms at presentation and lympho-vascular invasion.

# DISCUSSION

The study was conducted in a tertiary referral hospital in South India and the study population included adult clear cell and papillary renal cell carcinoma from January 2013 to December 2015. After applying the inclusion and exclusion criteria, the sample size was 171 cases, of which 102 were radical nephrectomies and 69 were partial nephrectomies.

## Case distribution:

Of the 171 cases, 158 were clear cell renal cell carcinoma and 13 were papillary renal cell carcinoma. Clear cell renal cell carcinoma constituted 92.3% of the study population with only 7.7% being papillary renal cell carcinoma. The prevalence of clear cell renal cell carcinoma worldwide is 70–80% of all renal cancers.(60) In one of the Indian studies, the prevalence of clear cell renal cell carcinoma was 67.7% when 617 patients diagnosed with renal cell carcinoma over a 12 year period were examined.(61)

## Demographic profile:

**Age and gender:**

The mean age distribution was 52.89 years with an overall range of 27 to 98 years and predominantly in the $5^{th}$ and $6^{th}$ decades of life. This compares well with two other studies from India with mean age being 55.15 and 52.79 years. (61, 62).

There was a male predominance in our study with 82% of the patients being males and male: female ratio of 4.5:1. A study of 75 cases by Ray R P et al showed that 68% were males with a male to female ratio of 2.1:1.(62)

**Mode of presentation:**

In our study 52% of the cases were detected incidentally while the remaining 48% were symptomatic at presentation. Among the cases that were detected incidentally, up to 75% belonged to pT1 stage thereby having a good prognosis. The result was different from a previous study done by Lee et al.(63) in which incidental and symptomatic presentation occurred in 57% and 42% of their cases, respectively. Their study also showed that patients who were symptomatic at presentation had an advanced disease thereby proving that the mode of presentation can independently predict an adverse patient outcome.

The Indian scenario has been depicted in a study by Jain et al (64) in which only 28.4% patients had an incidental diagnosis and 71.6% had symptomatic presentation. In our study, 52% patients had presented incidentally and this massive difference in the number of cases that presented incidentally might be explained by the fact that our institute is a tertiary referral centre and all cases that were detected incidentally elsewhere also ended up being operated here. Also the fact that there is an ever increasing use of radiological methods leads to more renal cell carcinomas being detected at an earlier stage before any symptoms develop. Overall, there has been a recent increase in incidental detection of renal cell carcinomas as stated in studies by Sunela KL et al(65) and Homma et al.(66)

**History of clinical presentation:**

Among the 82 patients who were symptomatic, 71% had complaints of haematuria. None of the cases in our study had the classic triad of renal mass, flank pain and haematuria as all of them had been picked up early. The next common symptom was flank pain. A study by Ares Valdes et al. (67) showed that hematuria was seen only in 24% of the patients.

**Co-morbidities:**

65% of the patients had co-existing medical illness of which 42% were hypertensives, 15% were diabetic and 36% were both hypertensive and diabetic. This is in line with other studies by Psutka SP et al. (68) where 13% of the patients had diabetes mellitus and it was independently associated with a decreased cancer specific and overall survival. Stojanovic M et al.(69) has proven that arterial hypertension may cause renal cell carcinoma and various other studies like Macleod LC et al(70) have also proven its causal relationship.

Gross parameters:

**Tumour focality:**

3.5% of the tumours within our study was multifocal. This was almost similar to a study by Crispen PL et al (71) where 5.4% of the total sample of patients had multifocal presentation of the disease.

**Type of nephrectomy:**

Of the 171 cases, 60% were radical nephrectomies while 40% were partial nephrectomies and there was no significant difference in overall survival between those two groups of patients. This was seen in concordance with a similar study by Thompson RH et al(72).

**Tumour size:**

In the present study, the tumour size varied from 1 to 14cm, with a mean of 5.99cm. This correlated with a study by Julian Dagher et al.(51) in which the tumour size ranged from 1cm to 17.5 cm with a mean size of 5 cm.

Histological parameters:

**Nuclear grading:**

In our study, we have tried to demonstrate the prognostic significance of WHO/ISUP grading and how it compares with the Fuhrman system. To an extent, ISUP system of grading allows us to identify the tumours that might behave aggressively even though it may be localised at the time of presentation and contrarily also to identify the ones that might have been predicted as higher risk for aggressive behavior by Fuhrman grading system but which in fact behave well. To our knowledge, in our country this is the first study that has tried to compare the WHO/ISUP and Fuhrman grading systems for clear cell and papillary RCC.

The mean follow up period in our study was 2 years and 7 months. In our series, we showed that grade 1 ISUP tumours were associated with a good prognosis, with an

exception of five cases, the remaining eighty five cases showing an event free survival in a follow-up period of up to 62.3 months. There was also a distinct separation of grades seen with respect to outcome for each of the WHO/ISUP grades 2, 3, and 4. (51)

Similar to our study, Ficarra *et al*. showed that Fuhrman nuclear grading had only moderate intra-observer reproducibility and noticed a substantial overlap in survival curves for G1 and G2 tumors thereby enabling them to cluster those categories, resulting in a three-tiered nuclear grading system and was an independent predictor of cause-specific survival in patients with conventional RCC.(73)

Many of the problems of Fuhrman grading which lead to a poor to, at best moderate inter and intra-observer agreement stems from the fact that a three-fold nature of the components are used to assign grading. This is due to the fact that the grading system assumes that for each case the grading subcategories also parallel with each other, thereby the higher-grade tumours having three high-grade subcategories and vice versa for the low-grade tumours having only low-grade sub-categories. Currently there are no clear guidelines as to how Fuhrman grading should be applied when there is a discordance among the three parameters. If this was the scenario, then the grades would have been given based on subjective assessment. (46,74,75)

Grades 1 to 3, by the WHO/ISUP grading criteria are based on the nucleolar features, with a characteristic nucleolar eosinophilia being mandatory for assigning a tumor either as grades 2 and 3.(52) This has resulted in a marked downgrading of cases when compared with the Fuhrman nuclear grading, especially with those assigned as

Fuhrman grade 2 which have been re assigned as ISUP grade 1 because of the absence of characteristic nucleoli.

Ever since the WHO/ISUP grading was accepted until now, there have been two validation studies done according to literature, although there have been no Indian studies. In a study by Cornejo KM et al(76) the ISUP nucleolar grade was found to be superior in predicting survival in patients with PRCC and also resulted in a significant downgrading of a number of tumours which were classified as Fuhrman grade 2.

For clear cell renal cell carcinomas, Khor et al(77)in their study from the Cleveland clinic showed that tumours with ISUP grades 1 to 3 had failed to significantly predict outcome and it was attributed to the fact that they had failed to define the area of tumour with the highest grade of tumour that would be utilized for grading purposes because of the intra-tumoral heterogeneity. They ended up using the criteria as 'The tumour grade was based on the highest grade present on the slide, even if focal'

Kim et al. in their study among 406 Japanese patients with ccRCC found that according to Fuhrman grading, there were 3 grade 1 tumors, 343 grade 2 tumors, 38 grade 3 tumors and 22 grade 4 tumors. The same when ISUP grade was applied showed 4 grade 1 tumors, 227 grade 2 tumors, 153 grade 3 tumors and 22 grade 4 tumors.(78)

Multivariate analysis in this study showed that ISUP grade was not significantly associated with event free survival ($p= 0.829$) , similar to the study by Kim et al.(78), however Dagher et al.(51) had found it to be significant.

There were no recurrence/metastases amongst patients with Fuhrman grade 1 tumours while 5 WHO/ISUP grade 1 tumour patients had recurrence/metastasis which was contrary to the study by Kim et al(78) where they had no recurrence or relapse.

But the interesting thing noted was that the cases which were subsequently downgraded to ISUP grade 1 from the Fuhrman grade 2 group exhibited a better prognosis compared with those cases that remained unchanged in the non-upgraded group. But similar such finding was not evident when analyzing cases in the Fuhrman grade 3 group.

The ISUP grading system was found to be superior to the Fuhrman grading system due to its diagnostic reproducibility and its ability to predict clinical outcomes.

# CONCLUSION

Conclusion:

- The overall agreement between the Fuhrman and ISUP grading systems was 92.79% with a weighted kappa of 0.5554.
- 96% cases assigned as Fuhrman nuclear grade 1 retained grade 1 by the ISUP grade.
- 38.5% cases of initial Fuhrman grade 2 retained grade 2 according to ISUP system, while 55% were assigned as ISUP grade 1 and 6.5% as ISUP grade 3.
- 39% cases assigned as Fuhrman grade 3 retained grade 3 according to ISUP system, while 39% cases were assigned as ISUP grade 2, 18% as ISUP grade 1 and 4% as ISUP grade 4.
- All cases with Fuhrman grade 4 retained grade 4 by ISUP grading.
- The mean age of presentation was 52.89 years with a male predominance. (Male : Female = 4.5:1)
- 52% cases were detected incidentally and among the symptomatic patients, 71% had a history of haematuria.
- The mean size of the tumors was 5.99cm ± 2.81cm.
- 89.47% patients were free of disease at the time of their last follow up with a mean disease free survival period of 4 years 11 months.
- 10.52% patients had metastasis, of which a subset of 28% also had concurrent loco regional recurrence of the disease.

- The clinical parameter with prognostic significance was the mode of initial presentation of the patient (p=0.011).
- The histopathological parameters with prognostic significance were found to be lymphovascular invasion (p<0.001), Fuhrman nuclear grading (p= 0.008) and ISUP (p= 0.0303) grading systems.
- To conclude, this retrospective study is the first among the Indian population with RCC to investigate the level of concordance between Fuhrman nuclear grading and the WHO/ISUP system and compare each system with their clinical follow up data.

Limitations of the study:

- Intra-tumoral heterogeneity is a proven factor in renal cell carcinoma which might cause a discrepancy in the study, as the tumors that have been given a lower grade might have had an un-sampled foci with a higher nuclear grade morphology and hence clinically behaved different than expected.
- The number of cases who had a positive event which included metastasis and recurrence were only 18. Hence, many histological parameters which had already been proven to be of significance in large scale studies were not statistically significant in our study.
- The mean follow up period in our study was only 2 years and 6 months which would not give us the whole picture of the behaviour of renal cell carcinomas, especially those which belonged to the lower grades. Hence, longer follow up period would be required to better predict their clinical behaviour.

- For estimation of survival analysis, only the information that was already available in the hospital electronic records were taken. It would have been more accurate if we were able to communicate with the patient till a particular point of time.

Future direction:

- ISUP grading system of renal cell carcinoma is here to stay for a long term because of its better reproducibility than Fuhrman grading while retaining its potential in determining prognostic significance.
- Grading of renal cell carcinomas has hereby been unified by the ISUP grading system which helps in multicentre studies.
- Large scale studies with a longer follow up period are further required to aid in determining the most apt and effective patient management strategies among the Indian population.

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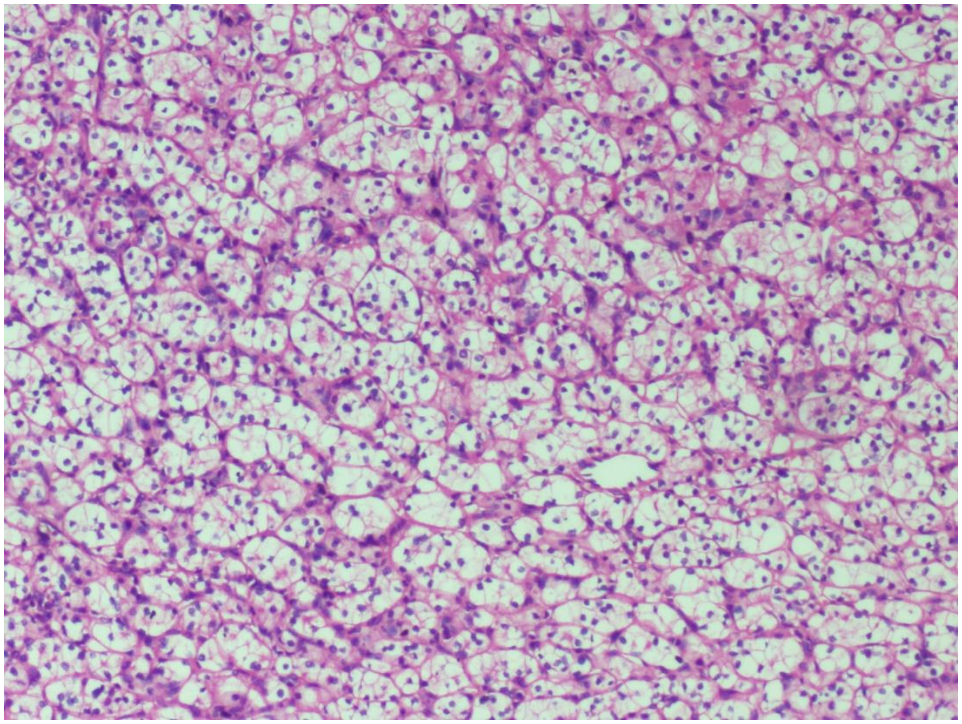
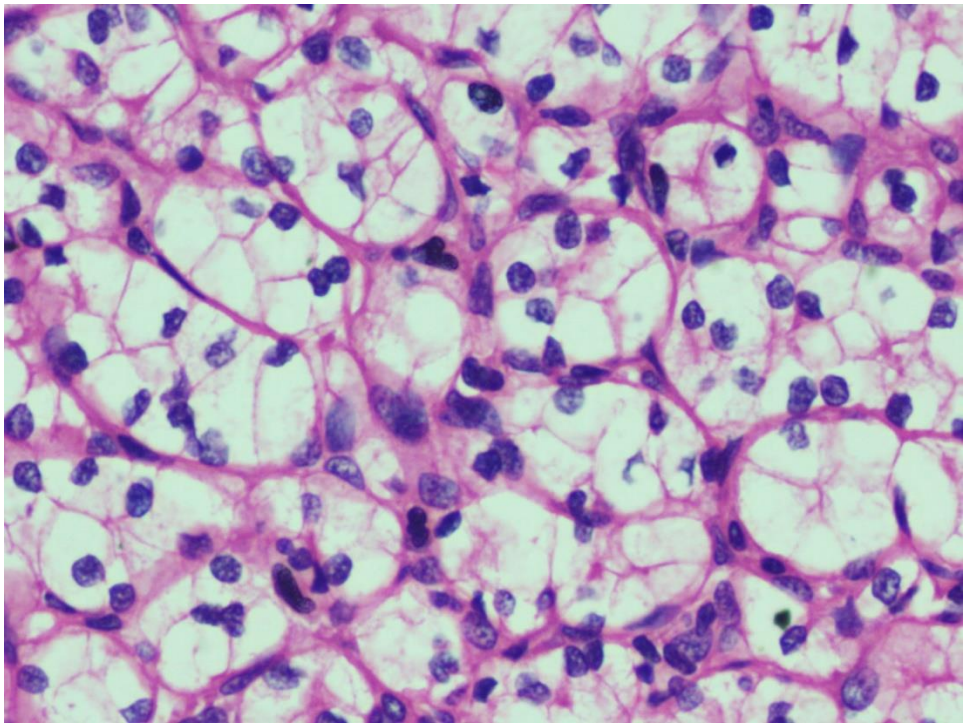
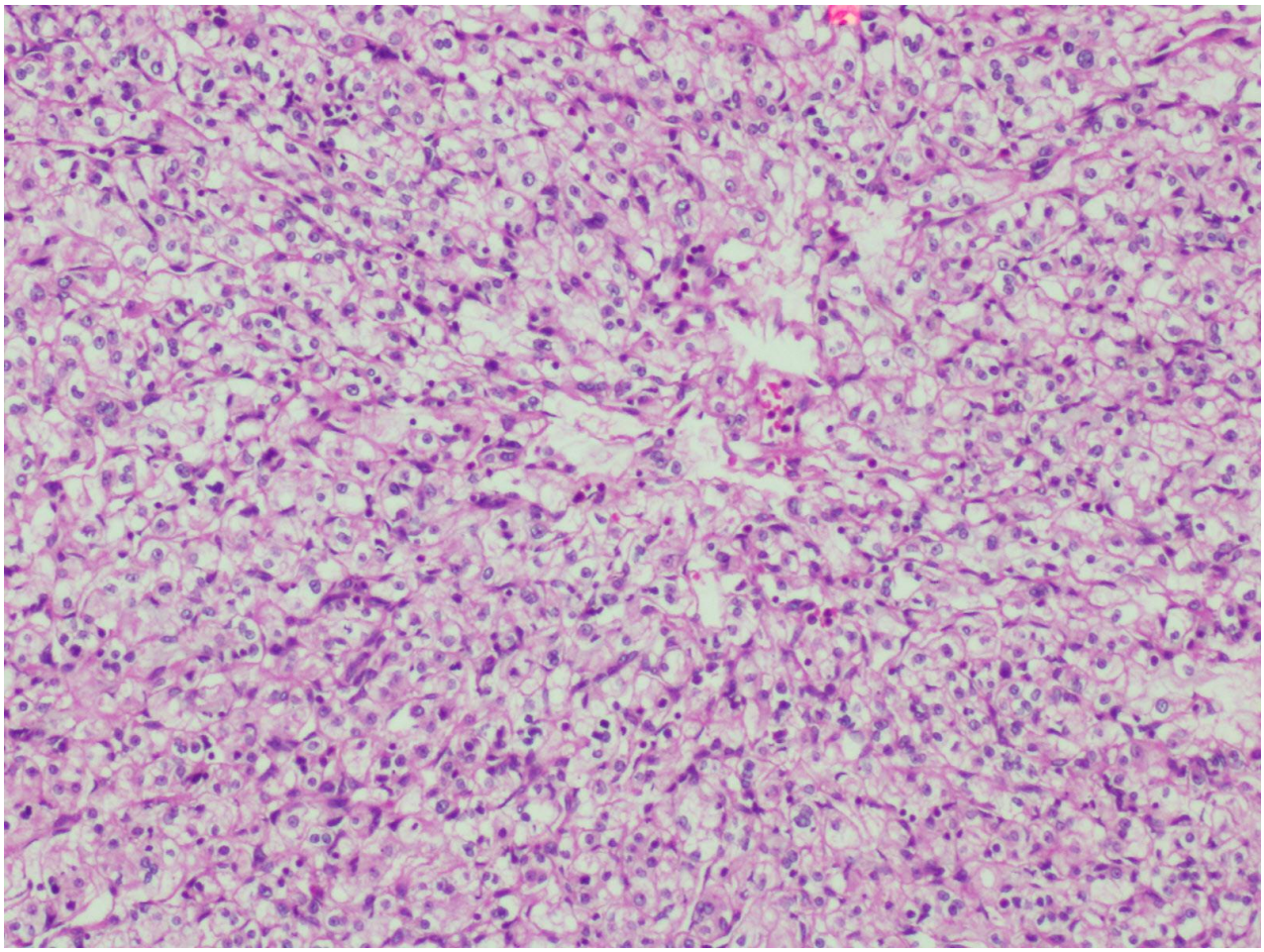


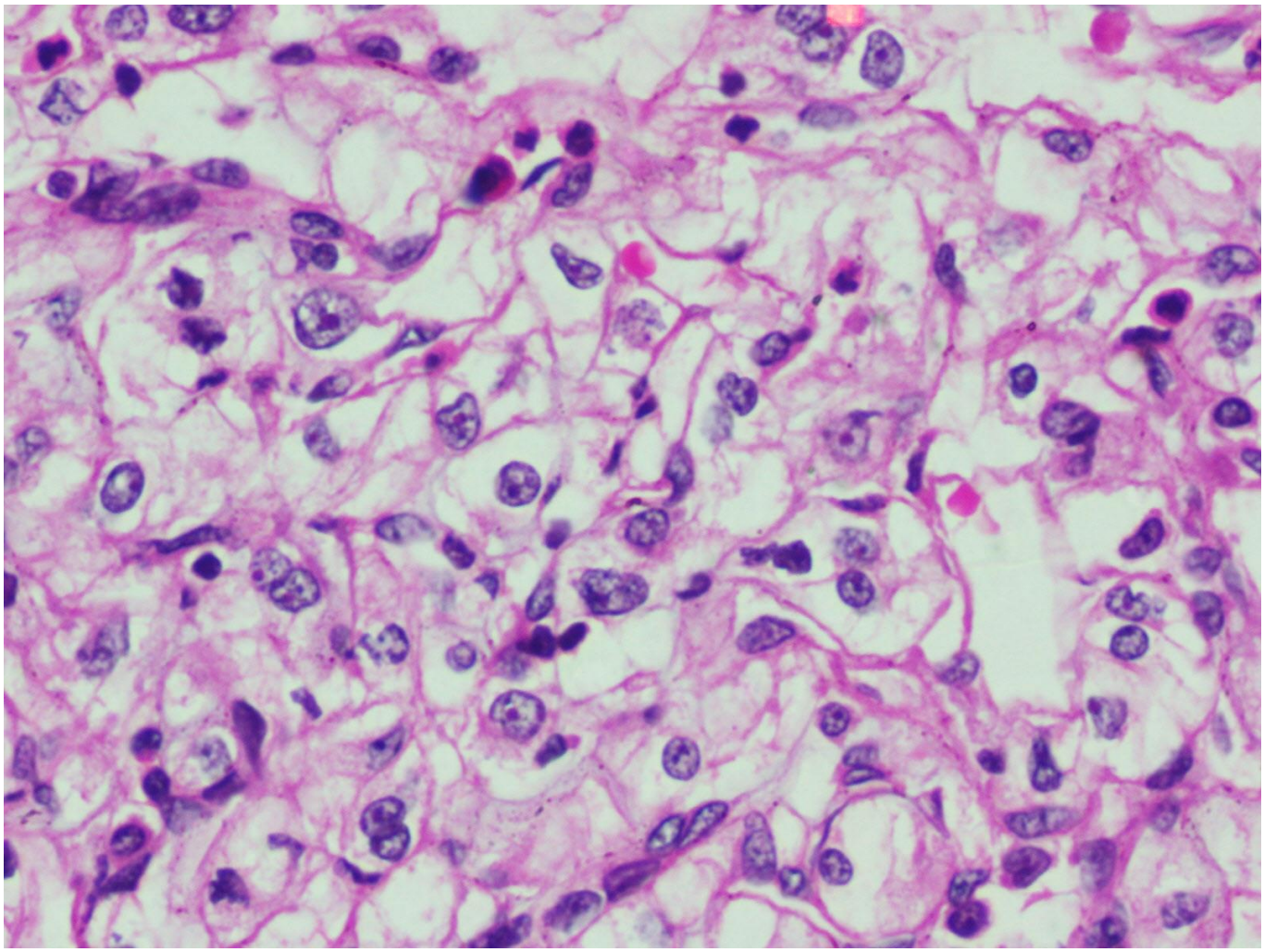
Clear cell renal cell carcinoma, ISUP grade 1, H&E 100x



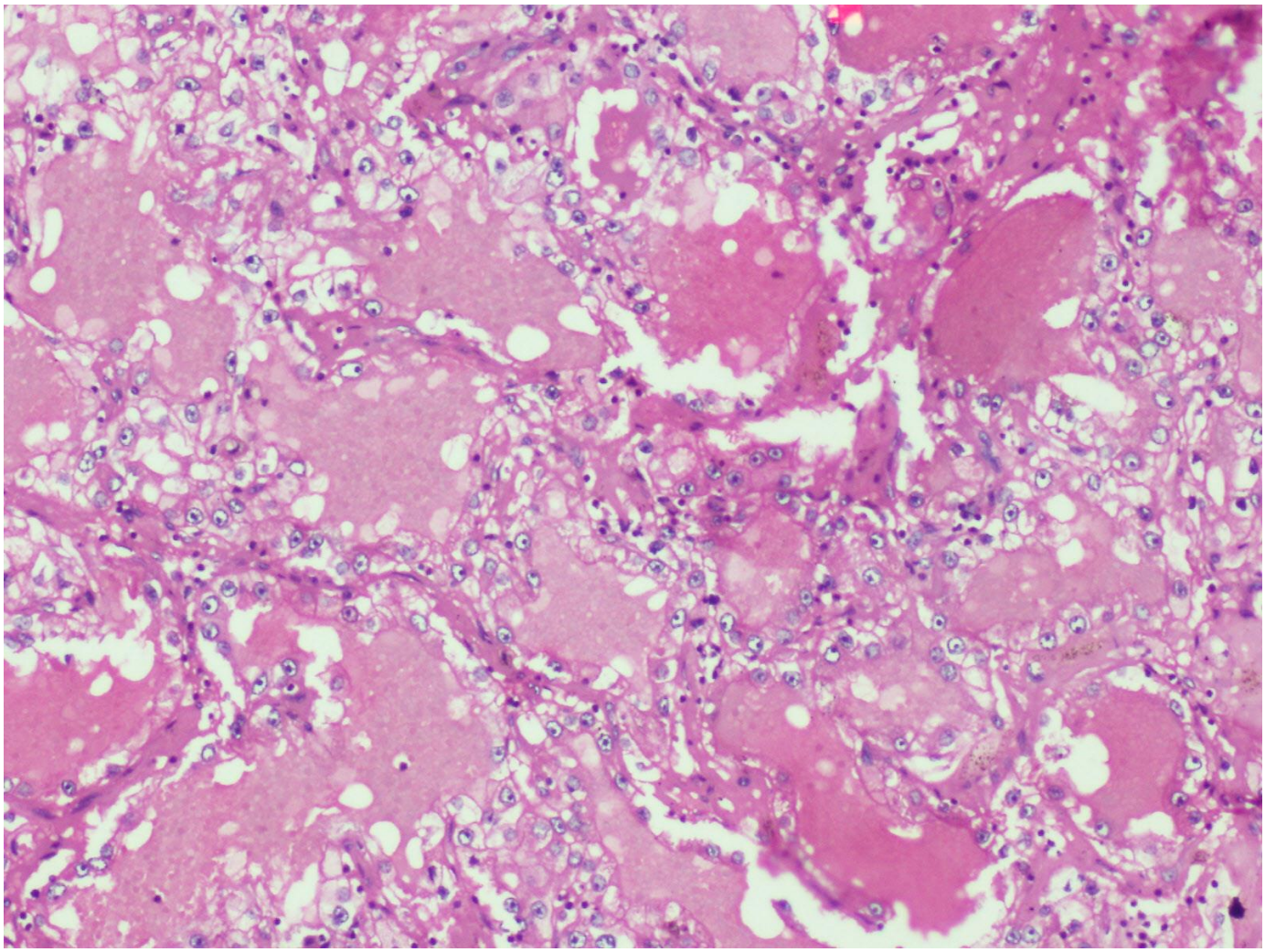
Clear cell renal cell carcinoma, ISUP grade 1: Inconspicuous/basophilic nucleoli, H&E 400x



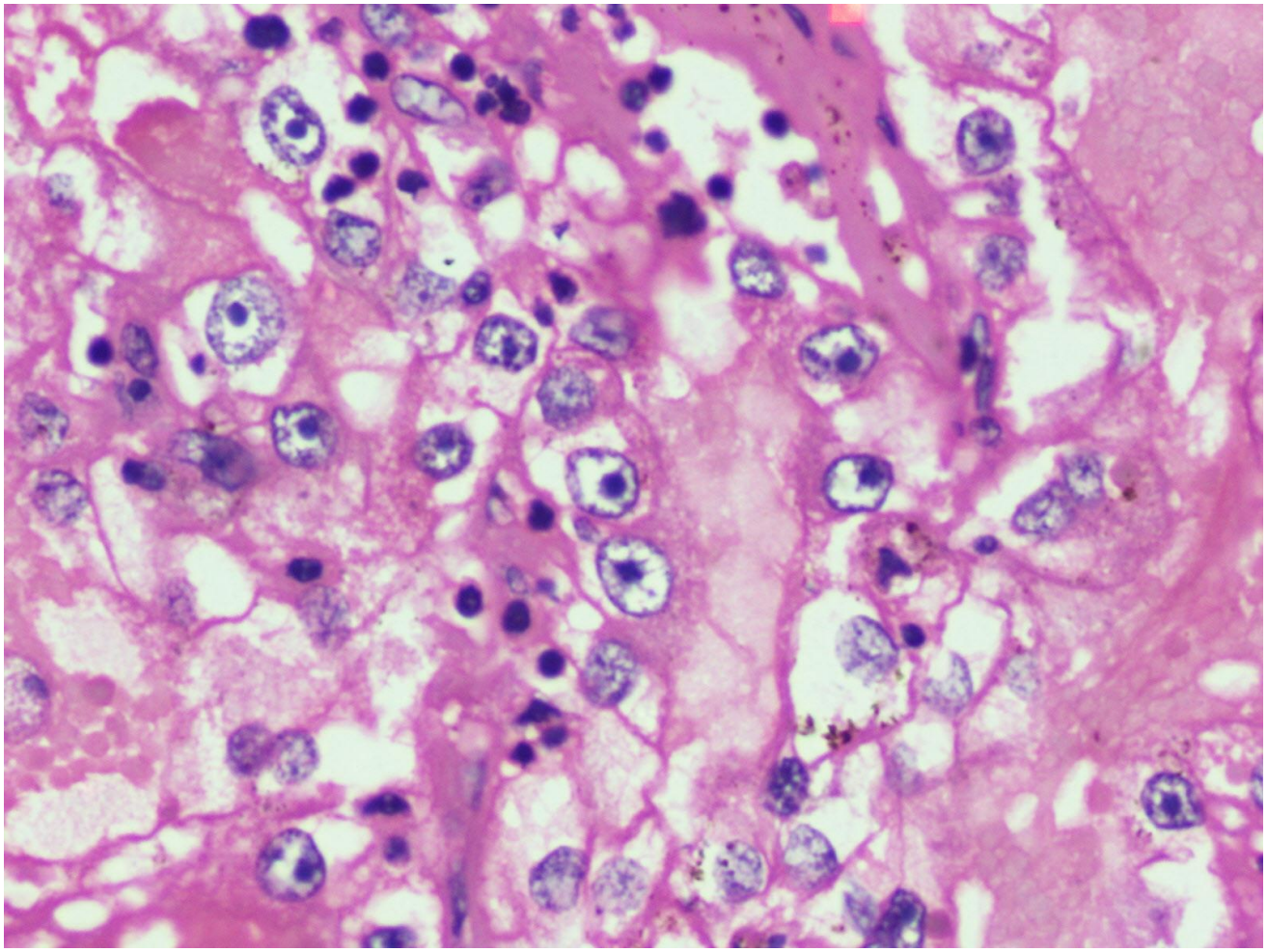
Clear cell renal cell carcinoma, ISUP grade 2: Visible nucleoli, H&E 100x



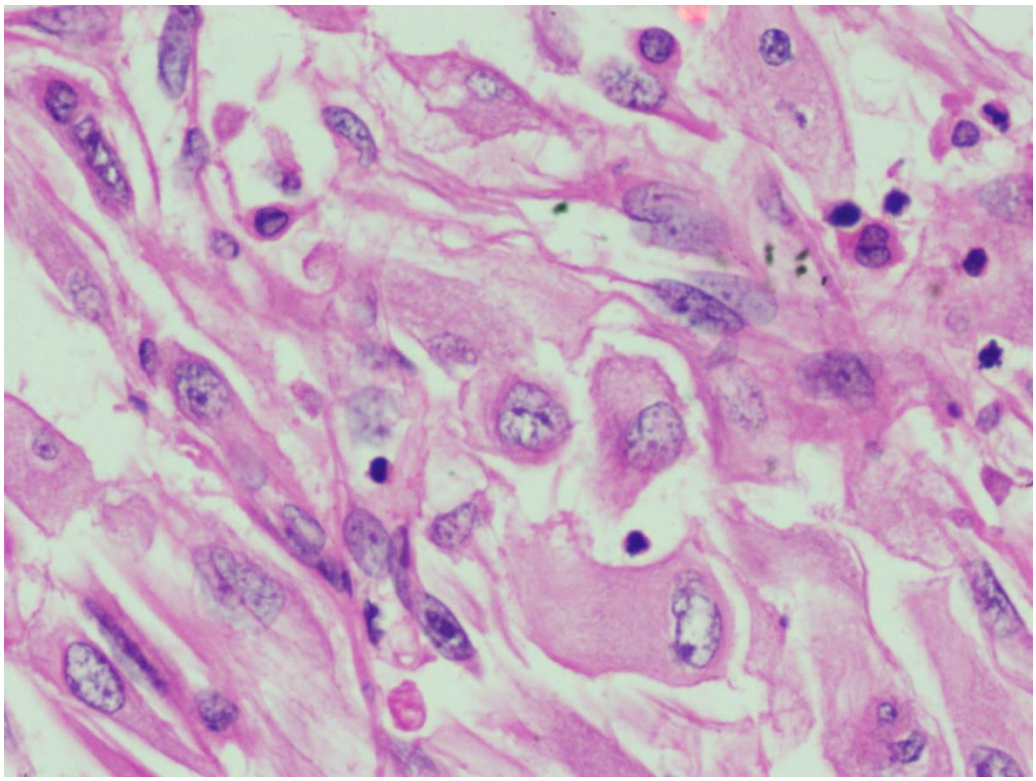
Clear cell renal cell carcinoma, ISUP grade 2: Eosinophilic nucleoli, H&E 400x



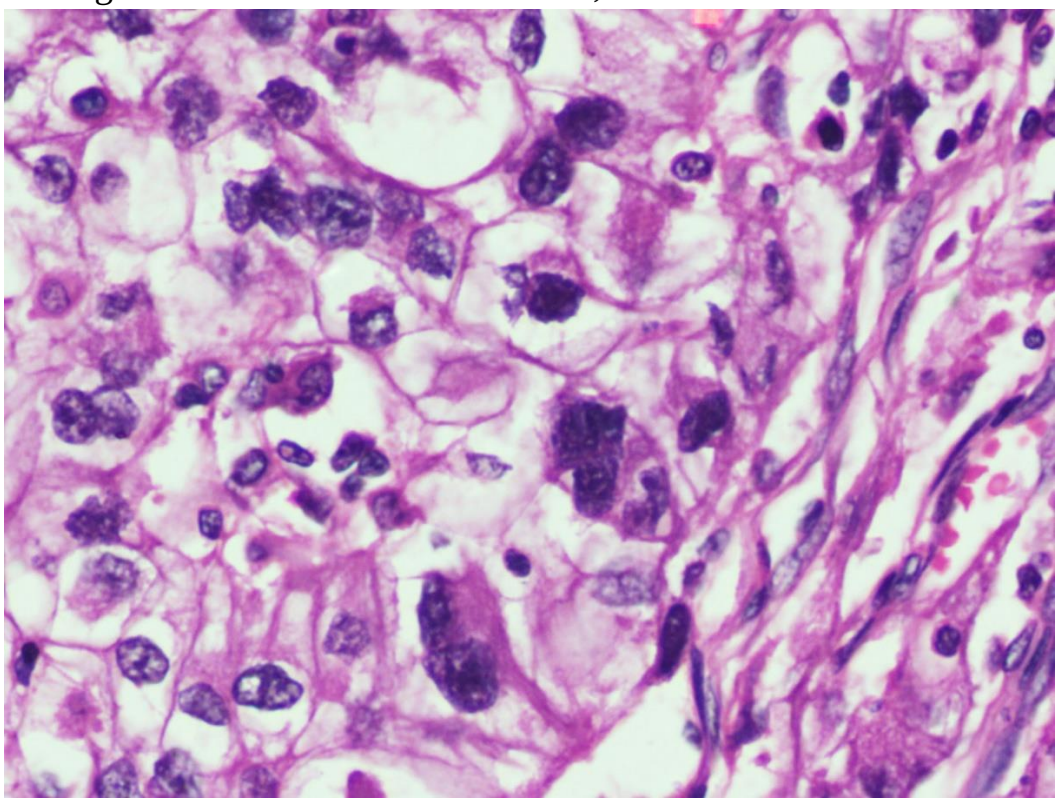
Clear cell renal cell carcinoma, ISUP grade 3: Prominent nucleoli, H&E 100x



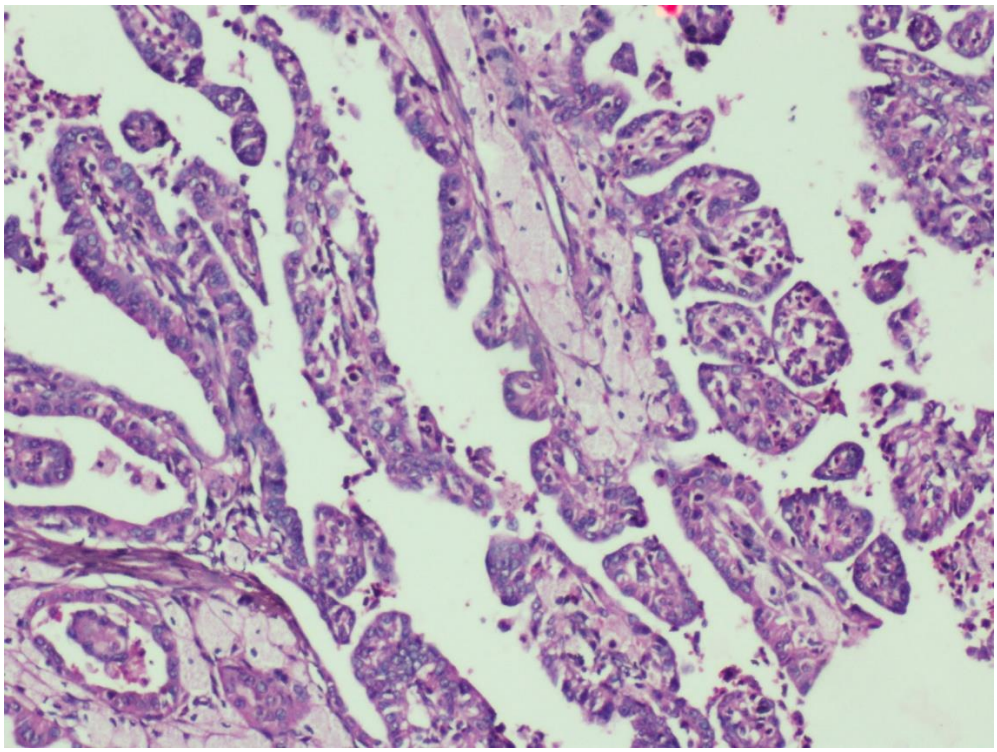
Clear cell renal cell carcinoma, ISUP grade 3: Prominent nucleoli, H&E 400x



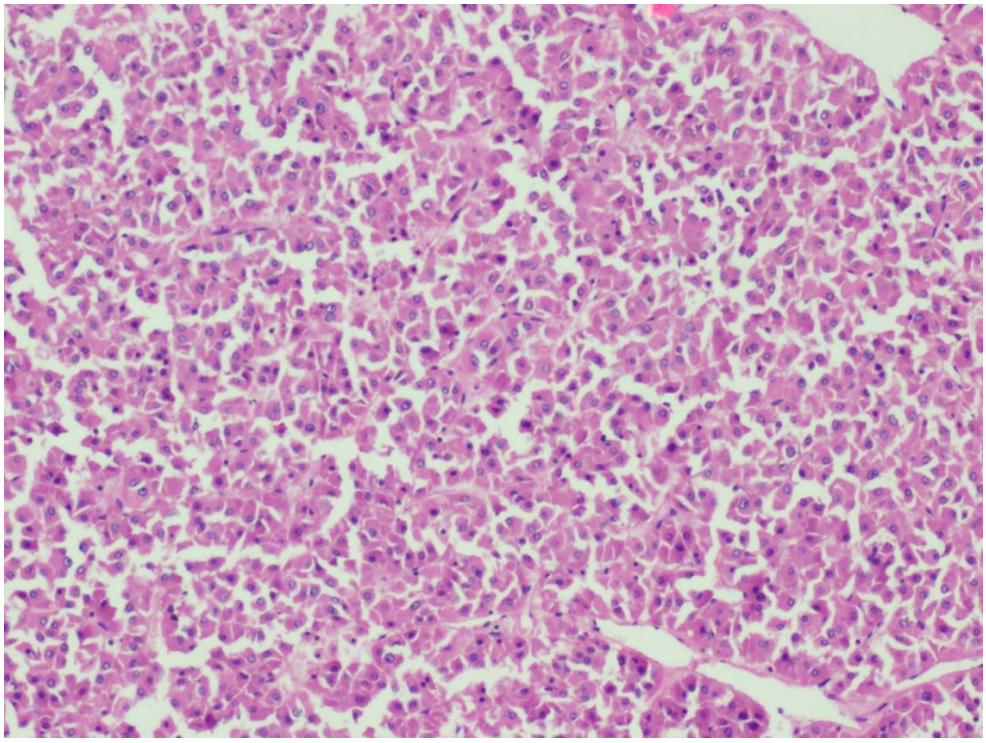
ISUP grade 4: Rhabdoid differentiation, H&E 400x



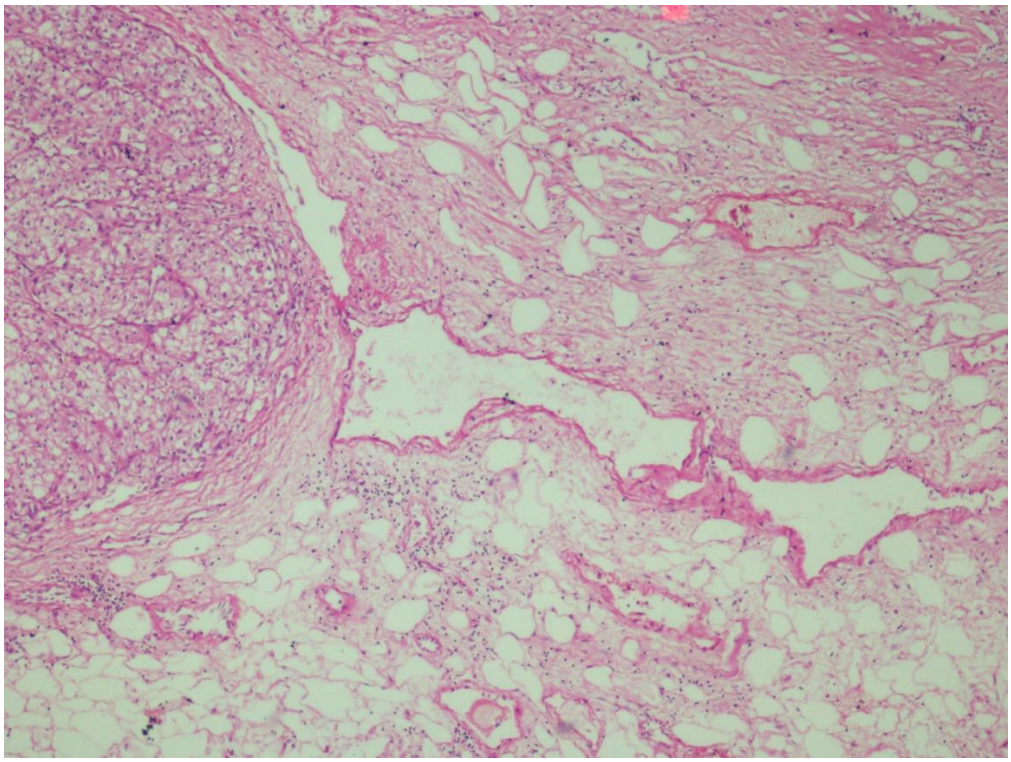
ISUP grade 4: Bizarre and Multinucleate giant tumour cells, H&E 400x



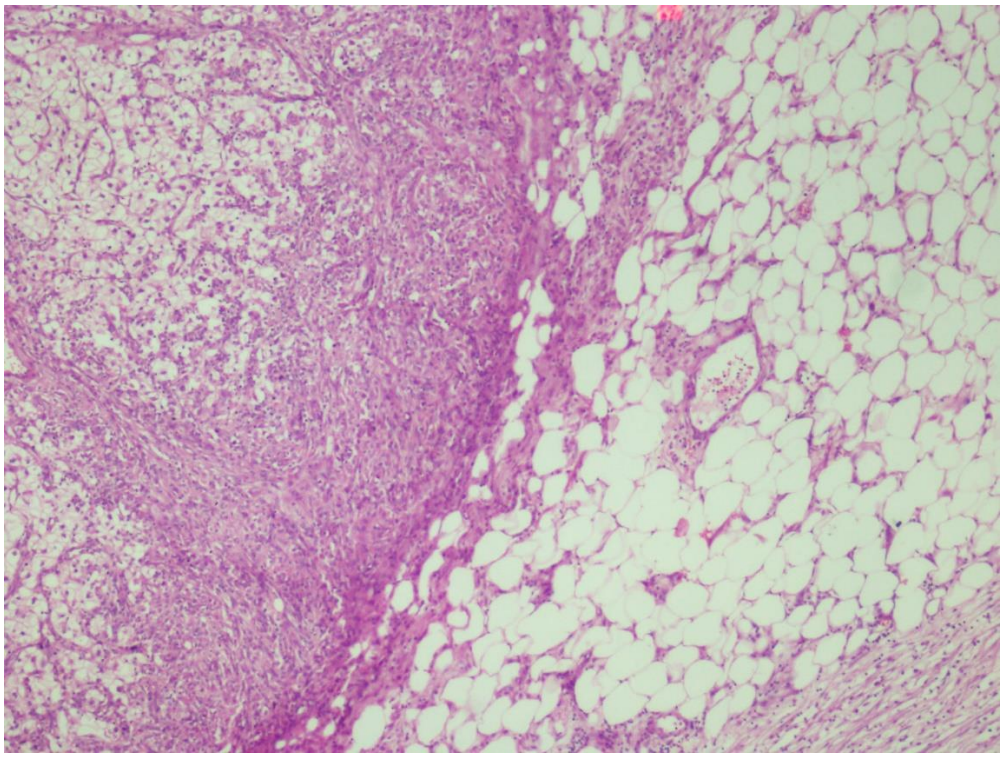
Papillary RCC type 1, H&E 100x



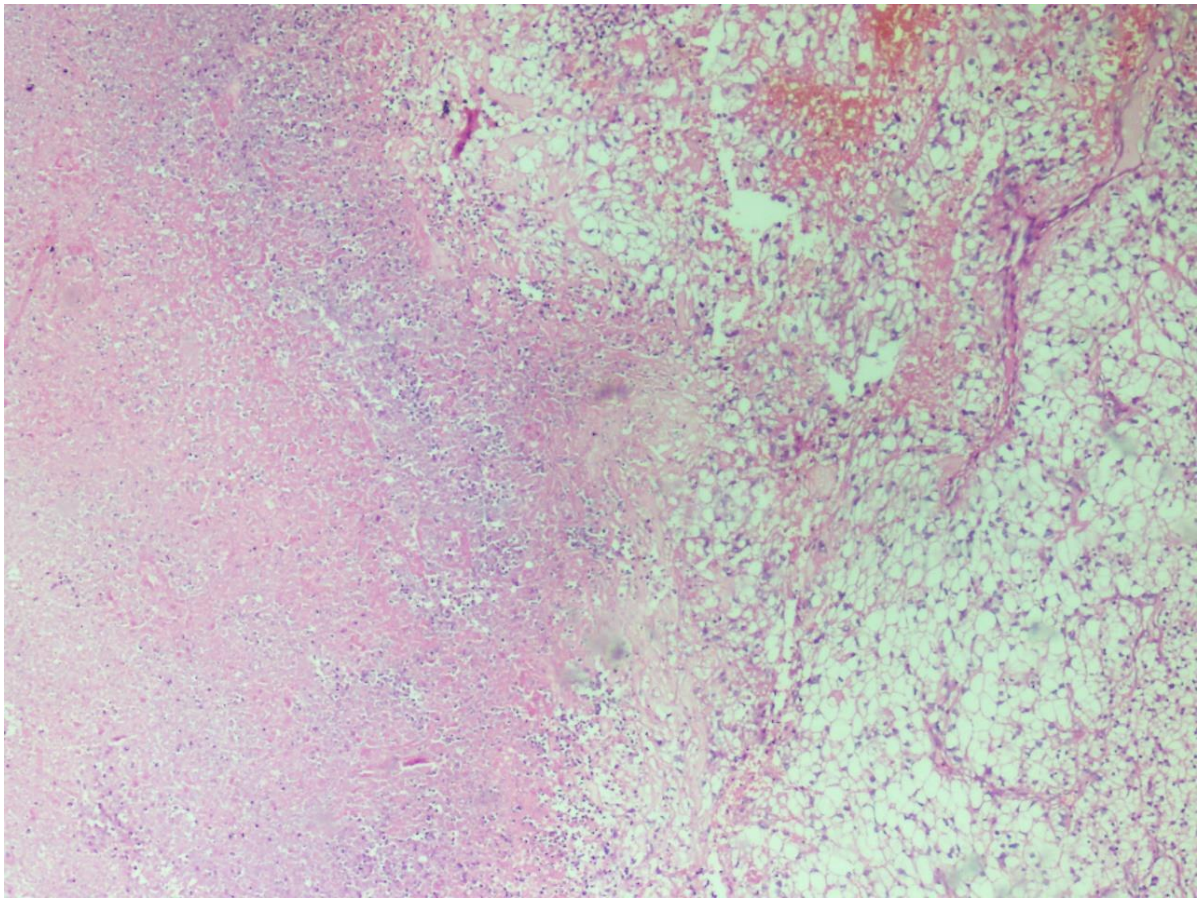
Papillary RCC type 2, H&E 100x



Sinus fat invasion, H&E 100x



Perinephric fat invasion, H&E 100x



Tumour necrosis, H&E 40x

# ANNEXURE – I

**LIST OF FIGURES:**

# ANNEXURE – II

**LIST OF TABLES:**

## ANNEXURE – III

# Procedure for staining:

- Place the slides in Xylene for 15 minutes
- Wash in graded alcohols (Absolute, 90% and 80% - each 2 dips)
- Next wash it in water for 5 minutes
- Place the slides in Haematoxylin for 5 minutes
- Wash it again in water for 5 minutes
- 2 dips in 1% acid alcohol
- Wash in water for 2 minutes
- 2 dips in Lithium carbonate for blueing
- Wash in water for 10 minutes
- After checking under microscope, dip in 80% alcohol
- Counterstain with eosin for 2 minutes
- Dehydrate in graded alcohols (90% and 80% absolute alcohol - each 2 dips)
- Clear in xylene
- Mount in D.P.X

## ANNEXURE – IV

# Proforma:

## Clinicopathological study of Renal Cell Carcinoma

Case No: Biopsy No: Hospital Number:

Age: Sex: M / F

Presentation:

- Incidentally detected : Y / N
- If symptomatic: Haematuria: Y/N; Flank pain: Y/N
- Other symptoms(if any):

Syndromic association (if any):

Co-morbidities: DM / HT / Others_____

Side involved: Right / Left .

Tumour focality: Unifocal / multifocal ( Number of foci - )

Post operative follow up period (in months) :

Recurrence: Yes / No; If yes, after ___ years.

Metastasis: Yes / No; If yes, At presentation / after____years

Gross findings:
Surgical specimen: Partial / Radical nephrectomy

Largest dimension of tumour (in cm):

Regional lymph nodes: Yes/No Other findings:

Histological findings:
Subtype: Clear / Papillary; If papillary; 1 / 2

| Tumour Grade | | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| Fuhrman | | | | | |
| ISUP | I | | | | |
| | II | | | | |
| | III | | | | |

If partial nephrectomy, resection margin involved: Y/N

Micro-vascular invasion: Y / N Tumour necrosis: Y / N

Capsular invasion: Y / N Perinephric fat invasion: Y / N;

Sinus fat invasion: Y / N Pelvicalyceal invasion: Y / N

Hilar vessel involvement: Y/N

LN involvement: Y/N; Tumour thrombus: Y/N; If yes, Renal vein/IVC

Other findings: Pathological stage:

# ANNEXURE – V (IRB documents)

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

**Dr. B.J. Prashantham,** M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

**Dr. Anna Benjamin Pulimood,** M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

**Dr. Biju George,** M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

September 09, 2017

Dr. Santhosh Raj A,
PG Registrar,
Department of General Pathology,
Christian Medical College,
Vellore – 632 002.

Sub: **Fluid Research Grant NEW PROPOSAL:**
A Clinicopathological study of adult renal cell carcinoma with comparison and re-grading of Fuhrman system with ISUP 2012 – A 3 year retrospective study.
Dr. Santhosh Raj A, (Employment Number: 21302) PG Registrar, Department of general pathology, Dr. Ramani Manoj Kumar, Employment Number: 10715, General Pathology, Dr. Anthony Devasia, Emp No: 09276, Urology unit 1Dr. Nitin Kekre, Urology.

Ref: **IRB Min. No. 10674 [OBSERVE] dated 01.06.2017**

Dear Dr. Santhosh Raj A,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Ramani Manoj Kumar, Dept. of General Pathology, CMC, Vellore



Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

**Dr. B.J. Prashantham,** M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

**Dr. Anna Benjamin Pulimood,** M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

**Dr. Biju George,** M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

September 09, 2017

Dr. Santhosh Raj A,
PG Registrar,
Department of General Pathology,
Christian Medical College,
Vellore – 632 002.

Sub: **Fluid Research Grant NEW PROPOSAL:**
A Clinicopathological study of adult renal cell carcinoma with comparison and re-grading of Fuhrman system with ISUP 2012 – A 3 year retrospective study.
Dr. Santhosh Raj A, (Employment Number: 21302) PG Registrar, Department of general pathology, Dr. Ramani Manoj Kumar, Employment Number: 10715, General Pathology. Dr. Anthony Devasia, Emp No: 09276, Urology unit 1Dr. Nitin Kekre, Urology.

Ref: **IRB Min. No. 10674 [OBSERVE] dated 01.06.2017**

Dear Dr. Santhosh Raj A,

The Institutional Review Board (**Blue**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "A Clinicopathological study of adult renal cell carcinoma with comparison and re- grading of Fuhrman system with ISUP 2012 – A 3 year retrospective study" on June 01st2017.

The Committee reviewed the following documents:

1. IRB Application format.
2. Wavier of Consent
3. Proforma
4. Cvs of Drs. Santhosh Raj A, Ramani Manoj Kumar, Anthony Devasia, Nitin Kekre
5. No. of documents 1 - 4.

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on June 01st2017 in the BRTC Conference Hall, Christian Medical College, Bagayam, Vellore 632002.



Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
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**Dr. Biju George,** M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

| Name | Qualification | Designation | Affiliation |
|---|---|---|---|
| Dr. Biju George | MBBS, MD, DM | Professor, Haematology, Research), Additional Vice Principal , Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC, Vellore | Internal, Clinician |
| Dr. B. J. Prashantham | MA(Counseling Psychology), MA (Theology), Dr. Min (Clinical Counselling) | Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore | External, Social Scientist |
| Dr. RatnaPrabha | MBBS, MD (Pharma) | Associate Professor, Clinical Pharmacology, CMC, Vellore | Internal, Pharmacologist |
| Dr. RekhaPai | BSc, MSc, PhD | Associate Professor, Pathology, CMC, Vellore | Internal, Basic Medical Scientist |
| Rev. Joseph Devaraj<br>Mrs. Sheela Durai | BSc, BD<br>MSc Nursing | Chaplaincy Department, CMC, Vellore<br>Professor, Medical Surgical Nursing, CMC, Vellore | Internal, Social Scientist<br>Internal, Nurse |
| Mr. C. Sampath | BSc, BL | Advocate, Vellore | External, Legal Expert |
| Ms. Grace Rebekha | M.Sc., (Biostatistics) | Lecturer, Biostatistics, CMC, Vellore | Internal, Statistician |
| Dr. Sowmya Sathyendra | MBBS, MD (Gen. Medicine) | Professor, Medicine III, CMC, Vellore | Internal, Clinician |
| Dr. Santhanam Sridhar | MBBS, DCH, DNB | Professor, Neonatology, CMC, Vellore | Internal, Clinician |
| Dr. Thomas V Paul | MBBS, MD, DNB, PhD | Professor,Endocrinology, CMC, Vellore | Internal, Clinician |
| Dr. SnehaVarkki | MBBS, DCH, DNB | Professor, Paediatrics, CMC, Vellore | Internal, Clinician |
| Dr. Sathish Kumar | MBBS, MD, DCH | Professor, Child Health, CMC, Vellore | Internal, Clinician |



Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
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Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

| | | | |
|---|---|---|---|
| Mrs. Emily Daniel | MSc Nursing | Professor, Medical Surgical Nursing, CMC, Vellore | Internal, Nurse |
| Dr. AjithSivadasan | MD, DM | Professor, Neurological Sciences, CMC, Vellore | Internal, Clinician |
| Dr. Visalakshi. J | MPH, PhD | Lecturer, Biostatistics, CMC, Vellore | Internal, Statistician |
| Mrs. Pattabiraman | BSc, DSSA | Social Worker, Vellore | External, Lay Person |
| Dr. Mathew Joseph | MBBS, MCH | Professor, Neurosurgery, CMC, Vellore | Internal, Clinician |
| Dr. Shyam Kumar NK | MBBS, DMRD, DNB, FRCR, FRANZCR | Professor, Radiology, CMC, Vellore | Internal, Clinician |
| Dr. Asha Solomon | MSc Nursing | Associate Professor, Medical SurgicalNursing, CMC, Vellore | Internal, Nurse |

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of Withdrawals for the study entitled: "A Clinicopathological study of adult renal cell carcinoma with comparison and re- grading of Fuhrman system with ISUP 2012 – A 3 year retrospective study" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

*Fluid Grant Allocation:*

*A sum of 30,000/- INR (Rupees Thirty thousand Only) will be granted for 24 months.*

Yours sincerely,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
M.B.B.S., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

IRB Min. No. 10674 [OBSERVE] dated 01.06.2017



Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

# ANNEXURE – VI

Data sheets:

| | slno | biopsyno | hospno | age | sex | inciden | haer | flanl | com | side | syndr | fuppe | meta | rec | re | surgical | largetumo | focality | hilar | histolog | papill | fuhr | isup | renal | lympho | tumornec | tumorper | pelvis | capsular | perinep | hilarves | tumortl | patholog |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 1 | 14511/13 | 455001f | 60 | 1 | 1 | | | 3 | 2 | 2 | 53 | 2 | 2 | | 1 | 2.5 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 3 | 2 | 13785/13 | 887531d | 53 | 1 | 1 | | | 1 | 1 | 2 | 64 | 2 | 2 | | 2 | 4 | 1 | 2 | 1 | | 3 | 3 | 2 | 2 | 1 | 5 | 2 | 2 | 2 | 2 | | 1 |
| 4 | 3 | 19044/13 | 486331f | 51 | 2 | 2 | 2 | 1 | 2 | 1 | 2 | 37 | 2 | 2 | | 2 | 4.2 | 1 | 1 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 5 | 4 | 9247/13 | 419369f | 58 | 1 | 2 | 1 | 2 | 3 | 1 | 2 | 40 | 2 | 2 | | 2 | 6.5 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 1 | 5 | 2 | 2 | 2 | 2 | | 2 |
| 6 | 5 | 15841/13 | 380473f | 58 | 1 | 2 | 1 | 2 | 3 | 1 | 2 | 48 | 2 | 2 | | 2 | 9.5 | 1 | 2 | 1 | | 3 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 3 |
| 7 | 6 | 17089/13 | 471659f | 42 | 2 | 1 | | | 3 | 2 | 2 | 12 | 2 | 2 | | 2 | 4.5 | 1 | 2 | 1 | | 2 | 1 | 2 | 1 | 1 | 5 | 2 | 2 | 2 | 2 | | 2 |
| 8 | 7 | 17152/13 | 465329f | 67 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 20 | 2 | 2 | | 1 | 9 | 1 | 2 | 1 | | 3 | 3 | 2 | 1 | 1 | 10 | 2 | 2 | 2 | 2 | | 3 |
| 9 | 8 | 15129/13 | 453043f | 68 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 60 | 2 | 2 | | 2 | 14 | 1 | 2 | 1 | | 3 | 4 | 1 | 2 | 1 | 40 | 2 | 1 | 2 | 2 | | 4 |
| 10 | 9 | 36432/13 | 494728f | 58 | 1 | 2 | 1 | 2 | 3 | 2 | 2 | 52 | 2 | 1 | 3 | 2 | 2.2 | 1 | 2 | 1 | | 3 | 3 | 2 | 2 | 1 | 5 | 2 | 2 | 2 | 2 | | 1 |
| 11 | 10 | 36106/13 | 682770f | 46 | 2 | 1 | | | | 1 | 2 | 51 | 2 | 2 | | 2 | 6 | 1 | 2 | 1 | | 3 | 1 | 1 | 2 | 2 | | 2 | 2 | 2 | 2 | | 5 |
| 12 | 11 | 5119/13 | 395192f | 44 | 1 | 1 | | | | 1 | 2 | 48 | 2 | 2 | | 1 | 3.5 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 13 | 12 | 7857/13 | 413206f | 42 | 1 | 2 | 2 | 1 | 3 | 1 | 2 | 63 | 2 | 2 | | 2 | 9.8 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 1 | 40 | 2 | 1 | 2 | 2 | | 3 |
| 14 | 13 | 11000/13 | 427230f | 54 | 1 | 1 | | | 2 | 2 | 2 | 12 | 2 | 2 | | 1 | 7 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 15 | 14 | 19952/13 | 488504f | 30 | 1 | 2 | 2 | 1 | 2 | 1 | 2 | 46 | 2 | 2 | | 2 | 3.6 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 16 | 15 | 18537/13 | 482759f | 61 | 2 | 1 | | | 3 | 1 | 2 | 12 | 2 | 2 | | 2 | 8.5 | 1 | 2 | 1 | | 3 | 1 | 2 | 2 | 2 | | 2 | 1 | 1 | 2 | | 5 |
| 17 | 16 | 13390/13 | 376787f | 47 | 1 | 1 | | | 3 | 2 | 2 | 12 | 2 | 2 | | 1 | 3.5 | 2 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 18 | 17 | 40905/13 | 718491f | 36 | 1 | 2 | 1 | 2 | | 1 | 2 | 12 | 2 | 2 | | 2 | 8 | 1 | 2 | 1 | | 3 | 2 | 2 | 2 | 1 | 20 | 2 | 2 | 2 | 2 | | 3 |
| 19 | 18 | 41067/13 | 709647f | 54 | 1 | 1 | | | 2 | 1 | 2 | 44 | 2 | 2 | | 1 | 4.3 | 2 | 2 | 1 | | 2 | 1 | 2 | 2 | 1 | 5 | 2 | 2 | 2 | 2 | | 2 |
| 20 | 19 | 12781/13 | 438516f | 44 | 1 | 2 | 2 | 1 | | 1 | 2 | 58 | 2 | 2 | | 1 | 2 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 60 | 2 | 2 | 2 | 2 | | 1 |
| 21 | 20 | 13115/13 | 439821f | 57 | 1 | 2 | 1 | 2 | 2 | 1 | 2 | 58 | 2 | 2 | | 2 | 8 | 1 | 2 | 1 | | 2 | 1 | 1 | 2 | 1 | 50 | 2 | 2 | 2 | 2 | 2 | 5 |
| 22 | 21 | 27057/13 | 628601f | 40 | 1 | 1 | | | | 2 | 2 | 36 | 2 | 2 | | 2 | 9.5 | 1 | 2 | 1 | | 3 | 1 | 1 | 1 | 1 | 10 | 2 | 1 | 2 | 1 | | 5 |
| 23 | 22 | 26959/13 | 629509f | 50 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 50 | 2 | 2 | | 2 | 8 | 1 | 2 | 1 | | 3 | 2 | 2 | 2 | 1 | 5 | 2 | 2 | 2 | 2 | | 3 |
| 24 | 23 | 26871/13 | 631855f | 58 | 2 | 1 | | | | 1 | 2 | 12 | 2 | 2 | | 2 | 4 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 25 | 24 | 23358/13 | 601732f | 58 | 1 | 1 | | | | 1 | 2 | 51 | 2 | 2 | | 2 | 8.5 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 3 |
| 26 | 25 | 22567/13 | 497517f | 52 | 1 | 2 | 1 | 2 | | 2 | 2 | 48 | 2 | 2 | | 2 | 9 | 1 | 2 | 1 | | 2 | 2 | 1 | 2 | 1 | 5 | 2 | 2 | 2 | 1 | 1 | 5 |
| 27 | 26 | 22357/13 | 600019f | 51 | 1 | 1 | | | 3 | 2 | 2 | 12 | 2 | 2 | | 2 | 7.5 | 1 | 2 | 1 | | 3 | 3 | 2 | 2 | 1 | 30 | 2 | 2 | 2 | 2 | | 3 |
| 28 | 27 | 25845/13 | 018951f | 83 | 1 | 1 | | | 2 | 2 | 2 | 19 | 2 | 2 | | 2 | 3.5 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 29 | 28 | 24290/13 | 607626f | 58 | 1 | 1 | | | 1 | 1 | 2 | 38 | 2 | 2 | | 2 | 4.5 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 30 | 29 | 21648/13 | 475130f | 34 | 1 | 2 | 2 | 1 | | 2 | 2 | 51 | 2 | 2 | | 1 | 4 | 1 | 2 | 1 | | 3 | 2 | 2 | 2 | 1 | 5 | 2 | 2 | 2 | 2 | | 1 |
| 31 | 30 | 43807/13 | 742103f | 60 | 1 | 2 | 1 | 2 | | 1 | 2 | 33 | 2 | 2 | | 2 | 6 | 1 | 2 | 2 | 1 | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 32 | 31 | 43526/13 | 708563f | 53 | 1 | 2 | 1 | 2 | 2 | 1 | 2 | 22 | 2 | 2 | | 2 | 3.9 | 1 | 2 | 1 | | 3 | 3 | 2 | 1 | 1 | 5 | 2 | 2 | 2 | 2 | | 1 |
| 33 | 32 | 39008/13 | 708366f | 62 | 1 | 2 | 1 | 2 | 2 | 1 | 2 | 12 | 2 | 2 | | 2 | 10.3 | 1 | 2 | 1 | | 2 | 2 | 1 | 2 | 1 | 30 | 1 | 1 | 1 | 2 | 1 | 5 |
| 34 | 33 | 41852/13 | 728135f | 42 | 1 | 1 | | | 3 | 1 | 2 | 34 | 2 | 2 | | 1 | 3.2 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 35 | 34 | 30528/13 | 652379f | 51 | 1 | 1 | | | 2 | 2 | 2 | 60 | 2 | 2 | | 2 | 7 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 1 | 40 | 2 | 2 | 2 | 2 | | 2 |

| | A | B | C | D | E | F | G | H | I | J | K | M | N | P | Q | R | S | T | U | V | W | X | Y | Z | AA | AB | AC | AD | AE | AF | AG | AH | AI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 36 | 35 | 40292/13 | 702103f | 54 | 1 | 1 | | | 1 | 1 | 2 | 36 | 2 | 2 | | 1 | 3.5 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 37 | 36 | 16290/13 | 457253f | 41 | 2 | 2 | 2 | 1 | | 1 | 2 | 51 | 2 | 2 | | 2 | 6 | 1 | 2 | 1 | | 1 | 2 | 2 | 2 | 1 | 10 | 2 | 2 | 2 | 2 | | 2 |
| 38 | 37 | 5625/13 | 392129f | 52 | 1 | 1 | | | 3 | 1 | 2 | 66 | 2 | 2 | | 2 | 10 | 1 | 2 | 1 | | 3 | 1 | 1 | 2 | 2 | | 2 | 1 | 1 | 2 | 1 | 6 |
| 39 | 38 | 19359/13 | 485171f | 59 | 1 | 1 | | | 3 | 2 | 2 | 62 | 2 | 2 | | 1 | 6 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 1 | 2 | 2 | | 2 |
| 40 | 39 | 2300/13 | 388138f | 66 | 1 | 1 | | | 3 | 1 | 2 | 12 | 2 | 2 | | 1 | 2.5 | 1 | 2 | 1 | | 3 | 3 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 41 | 40 | 4455/13 | 387949f | 49 | 1 | 2 | 1 | 1 | | 2 | 2 | 60 | 2 | 2 | | 2 | 6 | 1 | 2 | 1 | | 3 | 2 | 2 | 2 | 1 | 10 | 2 | 2 | 2 | 2 | | 2 |
| 42 | 41 | 5035/13 | 399997f | 65 | 1 | 1 | | | | 1 | 2 | 24 | 2 | 2 | | 1 | 2 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 43 | 42 | 28910/13 | 397317c | 62 | 1 | 1 | | | 2 | 1 | 2 | 56 | 2 | 2 | | 1 | 4.5 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 1 | 5 | 2 | 2 | 2 | 2 | | 2 |
| 44 | 43 | 4562/13 | 398046f | 67 | 1 | 2 | 1 | 2 | | 1 | 2 | 44 | 2 | 2 | | 2 | 3.5 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 45 | 44 | 13613/13 | 941362c | 98 | 1 | 1 | | | 2 | 2 | 2 | 60 | 1 | 2 | | 2 | 6.7 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 1 | 10 | 2 | 1 | 2 | 2 | | 2 |
| 46 | 45 | 27111/13 | 484474f | 66 | 1 | 1 | | | 3 | 1 | 2 | 32 | 2 | 2 | | 1 | 6.5 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 47 | 46 | 18891/13 | 462858f | 36 | 2 | 1 | | | | 2 | 2 | 12 | 2 | | 2 | 1 | 4 | 1 | 2 | 1 | | 2 | 3 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 48 | 47 | 38132/13 | 698956f | 59 | 1 | 1 | | | 2 | 1 | 2 | 52 | 2 | 2 | | 1 | 5.7 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 1 | 10 | 2 | 2 | 2 | 2 | | 2 |
| 49 | 48 | 37061/13 | 690555f | 54 | 1 | 2 | 1 | 2 | | 2 | 2 | 55 | 2 | 2 | | 1 | 2.5 | 1 | 2 | 1 | | 3 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 50 | 49 | 39511/13 | 708037f | 72 | 1 | 1 | | | 3 | 1 | 2 | 12 | 2 | 2 | | 1 | 4.2 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 51 | 50 | 43941/13 | 642949f | 55 | 1 | 1 | | | 3 | 2 | 2 | 12 | 2 | 2 | | 2 | 3.5 | 1 | 1 | 1 | | 3 | 1 | 2 | 2 | 2 | | 2 | 2 | 1 | 2 | | 5 |
| 52 | 51 | 41404/13 | 715610f | 60 | 1 | 2 | 1 | 2 | | 2 | 2 | 28 | 2 | 2 | | 2 | 10.5 | 1 | 2 | 1 | | 2 | 1 | 1 | 2 | 1 | 50 | 1 | 2 | 2 | 1 | 2 | 5 |
| 53 | 52 | 30698/13 | 512560d | 58 | 2 | 1 | | | 3 | 2 | 2 | 27 | 2 | 2 | | 1 | 3.6 | 1 | 2 | 1 | | 3 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 54 | 53 | 35532/13 | 673593f | 53 | 1 | 1 | | | 2 | 2 | 2 | 12 | 2 | 2 | | 1 | 6 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 55 | 54 | 1929/13 | 381200f | 53 | 1 | 2 | 1 | 2 | | 2 | 2 | 29 | 2 | 2 | | 2 | 13.5 | 1 | 2 | 1 | | 3 | 3 | 2 | 2 | 1 | 30 | 2 | 2 | 2 | 2 | | 4 |
| 56 | 55 | 35435/13 | 690519f | 73 | 1 | 1 | | | 2 | 2 | 2 | 27 | 1 | 2 | | 1 | 6 | 1 | 2 | 1 | | 3 | 3 | 2 | 2 | 1 | 5 | 2 | 2 | 2 | 2 | | 2 |
| 57 | 56 | 11551/13 | 433164f | 52 | 2 | 1 | | | 2 | 2 | 2 | 46 | 2 | 2 | | 2 | 5.7 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 58 | 57 | 40769/13 | 913984f | 58 | 1 | 1 | | | 1 | 2 | 2 | 42 | 2 | 2 | | 2 | 6 | 1 | 2 | 1 | | 3 | 3 | 2 | 2 | 2 | | 1 | 2 | 2 | 2 | | 2 |
| 59 | 58 | 23363/14 | 909516f | 50 | 1 | 2 | 1 | 2 | 1 | 1 | 2 | 24 | 2 | 2 | | 2 | 8.5 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 1 | 30 | 2 | 2 | 2 | 2 | | 3 |
| 60 | 59 | 15282/14 | 839406f | 55 | 1 | 2 | 2 | 1 | 3 | 2 | 2 | 51 | 2 | 2 | | 2 | 7 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 1 | 2 | 2 | 2 | | 2 |
| 61 | 60 | 13520/14 | | 74 | 1 | 2 | 1 | 2 | 2 | 1 | 2 | 36 | 2 | 2 | | 2 | 5.2 | 1 | 2 | 1 | | 2 | 1 | 1 | 2 | 1 | 5 | 1 | 2 | 2 | 2 | 1 | 5 |
| 62 | 61 | 17871/4 | 850071f | 58 | 1 | 1 | | | | 2 | 2 | 36 | 2 | 2 | | 1 | 5 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 63 | 62 | 20537/14 | 871341f | 37 | 1 | 2 | 1 | 2 | | 2 | 2 | 12 | 2 | 2 | | 2 | 5.2 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 64 | 63 | 38841/14 | 912428c | 54 | 2 | 2 | 1 | 2 | 2 | 1 | 1 | 30 | 1 | 1 | 1 | 1 | 3.2 | 2 | 2 | 1 | | 2 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 65 | 64 | 42868/14 | 061808g | 28 | 1 | 1 | | | | 2 | 2 | 32 | 2 | 2 | | 1 | 2.6 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | 2 | 1 |
| 66 | 65 | 43705/14 | 082942g | 37 | 1 | 2 | 1 | 2 | 3 | 1 | 2 | 38 | 2 | 2 | | 1 | 4.5 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 67 | 66 | 33899/14 | 025385g | 57 | 1 | 1 | | | 3 | 2 | 2 | 24 | 2 | 2 | | 2 | 7 | 1 | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 68 | 67 | 18267/14 | 846434d | 51 | 2 | 2 | 1 | 2 | 1 | 2 | 2 | 41 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 69 | 68 | 35082/14 | 038224g | 54 | 2 | 2 | 2 | 1 | | 1 | 2 | 45 | 2 | 2 | | 1 | 10.5 | 1 | 2 | 2 | 1 | 3 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 4 |
| 70 | 69 | 34999/14 | 858670f | 62 | 1 | 1 | | | 3 | 1 | 2 | 42 | 2 | 2 | | 1 | 2 | 1 | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |

| | A | B | C | D | E | F | G | H | I | J | K | M | N | P | Q | R | S | T | U | V | W | X | Y | Z | AA | AB | AC | AD | AE | AF | AG | AH | AI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 71 | 70 | 17611/14 | 815820f | 66 | 1 | 1 | | | 3 | 2 | 2 | 12 | 2 | 2 | | 2 | 6 | 2 | 2 | 1 | | 2 | 1 | 2 | 1 | 2 | | 2 | 2 | 1 | 2 | | 5 |
| 72 | 71 | 45261/13 | 769031f | 61 | 1 | 2 | 1 | 1 | | 1 | 2 | 12 | 1 | 2 | | 2 | 9 | 1 | 2 | 1 | | 3 | 2 | 2 | 2 | 2 | | 2 | 1 | 1 | 2 | | 5 |
| 73 | 72 | 40355/13 | 715138f | 59 | 1 | 2 | 1 | 2 | | 1 | 2 | 14 | 2 | 2 | | 1 | 3 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 74 | 73 | 41728/13 | 728560f | 44 | 1 | 1 | | | | 2 | 2 | 40 | 2 | 2 | | 1 | 3.8 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 75 | 74 | 27706/13 | 631651f | 55 | 1 | 2 | 1 | 2 | | 1 | 2 | 60 | 2 | 2 | | 2 | 6.5 | 1 | 2 | 1 | | 2 | 1 | 1 | 1 | 1 | 5 | 2 | 2 | 2 | 2 | 1 | 5 |
| 76 | 75 | 41938/13 | 716076f | 55 | 1 | 2 | 2 | 1 | 1 | 1 | 2 | 42 | 2 | 2 | | 1 | 3 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 77 | 76 | 29909/13 | 625033f | 46 | 2 | 1 | | | 2 | 1 | 2 | 48 | 2 | 2 | | 1 | 1.2 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 78 | 77 | 42589/14 | 076644g | 56 | 1 | 1 | | | 2 | 1 | 2 | 15 | 2 | 2 | | 1 | 3 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 79 | 78 | 42517/14 | 075015g | 68 | 2 | 1 | | | 3 | 1 | 2 | 32 | 2 | 2 | | 2 | 6.3 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 80 | 79 | 42518/14 | 080180g | 45 | 2 | 1 | | | 2 | 2 | 2 | 28 | 2 | 2 | | 2 | 8 | 1 | 2 | 1 | | 3 | 3 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 3 |
| 81 | 80 | 42849/14 | 077996g | 54 | 1 | 2 | 1 | 2 | 2 | 1 | 2 | 12 | 2 | 2 | | 2 | 7.3 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 3 |
| 82 | 81 | 41538/14 | 059121g | 36 | 1 | 1 | | | | 1 | 2 | 13 | 2 | 2 | | 1 | 4.2 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 83 | 82 | 44274/14 | 058656g | 42 | 1 | 1 | | | 3 | 2 | 2 | 42 | 2 | 2 | | 1 | 3 | 1 | 2 | 1 | | 2 | 3 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 84 | 83 | 38477/14 | 055841g | 25 | 2 | 2 | 1 | 2 | | 2 | 2 | 42 | 2 | 2 | | 1 | 8 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 1 | 10 | 2 | 1 | 2 | 2 | | 3 |
| 85 | 84 | 6597/14 | 790065f | 59 | 1 | 1 | | | 2 | 1 | 2 | 45 | 2 | 2 | | 1 | 5.5 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 86 | 85 | 8197/14 | 406858c | 43 | 1 | 2 | 2 | 1 | | 1 | 2 | 36 | 1 | 2 | | 1 | 4.5 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 87 | 86 | 5734/14 | 794182f | 64 | 1 | 2 | 1 | 2 | | 2 | 2 | 17 | 1 | 1 | 1 | 2 | 8.7 | 1 | 2 | 1 | | 3 | 1 | 2 | 1 | 1 | 20 | 1 | 2 | 2 | 2 | | 3 |
| 88 | 87 | 30765/14 | 022498g | 46 | 2 | 2 | 1 | 2 | | 2 | 2 | 24 | 2 | 2 | | 2 | 7.5 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 1 | 10 | 2 | 2 | 2 | 2 | | 3 |
| 89 | 88 | 12476/14 | 814794f | 39 | 1 | 1 | | | | 1 | 2 | 12 | 2 | 2 | | 1 | 2.5 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 1 | 2 | 2 | | 1 |
| 90 | 89 | 45088/14 | 088127g | 38 | 1 | 2 | 1 | 2 | | 1 | 2 | 36 | 2 | 2 | | 1 | 3.2 | 1 | 2 | 1 | | 2 | 3 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 91 | 90 | 5725/14 | 794942f | 58 | 1 | 1 | | | 2 | 1 | 2 | 36 | 2 | 2 | | 2 | 8 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 3 |
| 92 | 91 | 40260/14 | 794942f | 55 | 1 | 1 | | | | 2 | 2 | 37 | 2 | 2 | | 1 | 1.5 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 93 | 92 | 35735/14 | 087738f | 42 | 2 | 1 | | | | 1 | 1 | 48 | 2 | 2 | | 1 | 5.4 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 94 | 93 | 34428/14 | 033936g | 60 | 1 | 1 | | | 3 | 1 | 2 | 36 | 2 | 2 | | 2 | 6.5 | 1 | 2 | 1 | | 2 | 2 | 1 | 1 | 2 | | 2 | 2 | 2 | 2 | 2 | 6 |
| 95 | 94 | 11826/14 | 819860f | 50 | 2 | 1 | | | 3 | 1 | 2 | 48 | 2 | 2 | | 1 | 3.8 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 96 | 95 | 45028/13 | 761214f | 52 | 1 | 2 | 1 | 2 | 3 | 2 | 2 | 28 | 2 | 2 | | 1 | 4.3 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 97 | 96 | 45098/13 | 747461f | 63 | 1 | 1 | | | | 1 | 2 | 24 | 2 | 2 | | 2 | 7 | 1 | 2 | 1 | | 2 | 2 | 1 | 2 | 2 | | 2 | 2 | 2 | 2 | | 5 |
| 98 | 97 | 29010/14 | 913162f | 51 | 2 | 1 | | | | 1 | 2 | 44 | 2 | 2 | | 2 | 6 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 99 | 98 | 29847/14 | 788323f | 58 | 1 | 1 | | | 2 | 2 | 2 | 38 | 2 | 2 | | 1 | 2.8 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 100 | 99 | 32709/14 | 031480g | 57 | 1 | 1 | | | 3 | 1 | 2 | 20 | 2 | 2 | | 2 | 6.5 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 101 | 100 | 22206/14 | 871202f | 32 | 2 | 1 | | | | 2 | 2 | 43 | 2 | 2 | | 2 | 4.2 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 102 | 101 | 33587/14 | 647189c | 54 | 1 | 1 | | | 3 | 1 | 2 | 31 | 2 | 2 | | 2 | 7.5 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 2 | | 1 | 2 | 2 | 2 | 1 | 5 |
| 103 | 102 | 31315/14 | 912778f | 27 | 2 | 2 | 1 | 2 | | 2 | 2 | 29 | 2 | 2 | | 2 | 13.5 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 1 | 10 | 2 | 2 | 2 | 2 | | 4 |
| 104 | 103 | 27290/14 | 899402f | 50 | 1 | 2 | 1 | 2 | 1 | 1 | 2 | 12 | 2 | 2 | | 2 | 5.5 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | 1 | 5 |
| 105 | 104 | 26044/14 | 891801f | 48 | 1 | 1 | | | | 1 | 2 | 40 | 2 | 2 | | 1 | 5.5 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |

| | A | B | C | D | E | F | G | H | I | J | K | M | N | P | Q | R | S | T | U | V | W | X | Y | Z | AA | AB | AC | AD | AE | AF | AG | AH | AI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 106 | 105 | 25163/14 | 889831f | 50 | 1 | 1 | | | 3 | 2 | 2 | 29 | 2 | 2 | | 2 | 6.4 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 107 | 106 | 560/14 | 298421d | 45 | 1 | 2 | 1 | 2 | | 2 | 2 | 44 | 2 | 2 | | 2 | 6.2 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 108 | 107 | 24643/14 | 812052f | 48 | 1 | 1 | | | 3 | 1 | 2 | 20 | 2 | 2 | | 1 | 2.5 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 109 | 108 | 11415/14 | 821649f | 37 | 1 | 2 | 2 | 1 | | 1 | 2 | 33 | 2 | 2 | | 2 | 5.7 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 110 | 109 | 4961/14 | 968152c | 59 | 1 | 1 | | | 2 | 1 | 2 | 12 | 2 | 2 | | 1 | 1 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 111 | 110 | 4957/14 | 575087a | 52 | 1 | 1 | | | 2 | 2 | 2 | 48 | 2 | 2 | | 1 | 1.6 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 112 | 111 | 752/14 | 746997f | 47 | 1 | 1 | | | 2 | 1 | 2 | 31 | 2 | 2 | | 1 | 1.8 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 113 | 112 | 29911/13 | 646311f | 60 | 2 | 2 | 1 | 1 | | 1 | 2 | 49 | 2 | 2 | | 2 | 7.5 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 3 |
| 114 | 113 | 22193/13 | 601258f | 28 | 1 | 2 | 2 | 1 | | 1 | 2 | 33 | 1 | 2 | | 1 | 3.5 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 115 | 114 | 3382/13 | 365663f | 59 | 1 | 2 | 1 | 2 | 2 | 2 | 2 | 62 | 2 | 2 | | 2 | 11.5 | 1 | 1 | 2 | 1 | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 4 |
| 116 | 115 | 27370/13 | 632784f | 53 | 1 | 1 | | | 2 | 2 | 2 | 43 | 2 | 2 | | 1 | 7 | 1 | 2 | 2 | 1 | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 117 | 116 | 28654/13 | 370569c | 59 | 1 | 1 | | | 3 | 1 | 2 | 25 | 2 | 2 | | 1 | 4.5 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 118 | 117 | 22204/14 | 453043f | 69 | 1 | 1 | | | 2 | 1 | 2 | 36 | 2 | 2 | | 1 | 3.7 | 1 | 2 | 1 | | 3 | 3 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 119 | 118 | 44939/14 | 088475g | 55 | 1 | 2 | 1 | 2 | 1 | 2 | 2 | 24 | 2 | 2 | | 1 | 3.2 | 1 | 2 | 2 | 1 | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 120 | 119 | 16231/14 | 806630f | 64 | 1 | 1 | | | 1 | 2 | 2 | 24 | 2 | 2 | | 1 | 4.5 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 121 | 120 | 46250/14 | 087507g | 62 | 1 | 1 | | | 3 | 2 | 2 | 12 | 2 | 2 | | 2 | 5.3 | 1 | 2 | 1 | | 3 | 2 | 2 | 2 | 1 | 10 | 2 | 1 | 2 | 2 | | 2 |
| 122 | 121 | 48234/14 | 095441g | 54 | 1 | 2 | 1 | 2 | 2 | 1 | 2 | 24 | 2 | 2 | | 2 | 6 | 1 | 2 | 1 | | 3 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 123 | 122 | 43321/14 | 051399g | 56 | 2 | 1 | | | 2 | 2 | 2 | 48 | 2 | 2 | | 2 | 7.4 | 1 | 1 | 1 | | 2 | 2 | 1 | 2 | 2 | | 2 | 2 | 1 | 2 | | 5 |
| 124 | 123 | 26132/14 | 895160f | 55 | 1 | 1 | | | | 2 | 2 | 36 | 2 | 2 | | 2 | 7.5 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 3 |
| 125 | 124 | 47622/14 | 078315g | 60 | 1 | 1 | | | 1 | 2 | 2 | 12 | 2 | 2 | | 1 | 3.2 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 126 | 125 | 46994/14 | 102308g | 51 | 1 | 2 | 2 | 1 | | 2 | 2 | 24 | 2 | 2 | | 2 | 5 | 1 | 1 | 1 | | 3 | 3 | 2 | 2 | 1 | 30 | 2 | 1 | 2 | 2 | 1 | 5 |
| 127 | 126 | 48941/14 | 256869f | 59 | 1 | 1 | | | 1 | 2 | 2 | 36 | 1 | 1 | 1 | 2 | 11 | 1 | 1 | 1 | | 3 | 4 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | 1 | 6 |
| 128 | 127 | 28488/14 | 899268f | 51 | 1 | 2 | 1 | 2 | 2 | 1 | 2 | 48 | 1 | 2 | | 2 | 6 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 129 | 128 | 15988/15 | 203887g | 45 | 2 | 1 | | | | 2 | 2 | 12 | 2 | 2 | | 2 | 6.5 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 130 | 129 | 13122/15 | 169280g | 53 | 1 | 1 | | | 2 | 1 | 2 | 24 | 2 | 2 | | 1 | 5 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 131 | 130 | 6408/15 | 141464g | 60 | 1 | 2 | 1 | 2 | | 2 | 2 | 36 | 2 | 2 | | 2 | 13 | 1 | 1 | 1 | | 2 | 2 | 1 | 2 | 1 | 40 | 2 | 2 | 2 | 2 | 1 | 5 |
| 132 | 131 | 9803/15 | 156811g | 64 | 1 | 2 | 1 | 2 | 1 | 1 | 2 | 12 | 1 | 2 | | 2 | 12 | 1 | 2 | 1 | | 3 | 2 | 2 | 1 | 2 | | 2 | 2 | 1 | 2 | | 5 |
| 133 | 132 | 5376/13 | 405914f | 47 | 1 | 2 | 1 | 2 | | 1 | 2 | 12 | 1 | 2 | | 2 | 8 | 1 | 1 | 1 | | 3 | 2 | 1 | 1 | 1 | 10 | 1 | 1 | 2 | 2 | 2 | 6 |
| 134 | 133 | 33747/13 | 681659f | 55 | 1 | 2 | 1 | 2 | | 2 | 2 | 36 | 2 | 2 | | 2 | 7 | 1 | 1 | 1 | | 2 | 3 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 135 | 134 | 22719/13 | 602693f | 53 | 1 | 2 | 1 | 2 | | 2 | 2 | 36 | 2 | 2 | | 2 | 9 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 3 |
| 136 | 135 | 2054/15 | 100343g | 64 | 1 | 1 | | | 2 | 2 | 2 | 12 | 2 | 2 | | 2 | 5.2 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 1 | 10 | 2 | 2 | 2 | 2 | | 2 |
| 137 | 136 | 9137/15 | 196458f | 62 | 1 | 2 | 1 | 2 | | 2 | 2 | 24 | 2 | 2 | | 1 | 3.5 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 138 | 137 | 7284/15 | 155871g | 59 | 1 | 1 | | | 1 | 1 | 2 | 24 | 2 | 2 | | 1 | 8 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 1 | 10 | 2 | 2 | 2 | 2 | | 3 |
| 139 | 138 | 6362/15 | 946104f | 58 | 1 | 1 | | | 3 | 1 | 2 | 12 | 2 | 2 | | 2 | 5.5 | 1 | 2 | 1 | | 3 | 3 | 1 | 1 | 2 | | 2 | 2 | 2 | 2 | 1 | 5 |
| 140 | 139 | 26885/15 | 305860f | 51 | 1 | 2 | 2 | 1 | 3 | 2 | 2 | 12 | 2 | 2 | | 2 | 9.5 | 1 | 1 | 1 | | 3 | 3 | 2 | 2 | 2 | | 2 | 2 | 2 | 1 | | 5 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 141 | 140 | 24423/15 | 631936f | 28 | 1 | 1 | | | 2 | 1 | 30 | 2 | 2 | 1 | 2.7 | 1 | 2 | 1 | | 3 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 142 | 141 | 14127/15 | 575353c | 29 | 2 | 2 | 1 | 2 | | 2 | 2 | 39 | 2 | 2 | 2 | 7 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 1 | 10 | 2 | 2 | 2 | 2 | | 2 |
| 143 | 142 | 18059/15 | 177655g | 41 | 1 | 1 | | | 1 | 2 | 2 | 31 | 2 | 2 | 1 | 4.3 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 144 | 143 | 16982/15 | 207146g | 51 | 1 | 1 | | | 3 | 1 | 2 | 33 | 2 | 2 | 1 | 4 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 145 | 145 | 28409/15 | 254003g | 70 | 1 | 1 | | | 3 | 2 | 2 | 24 | 2 | 2 | 2 | 9.5 | 2 | 1 | 1 | | 4 | 4 | 2 | 2 | 1 | 20 | 2 | 2 | 2 | 2 | | 3 |
| 146 | 146 | 35448/15 | 262373g | 65 | 1 | 2 | 1 | 2 | 2 | 1 | 2 | 32 | 2 | 2 | 2 | 6 | 1 | 1 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 1 | 2 | 2 | | 2 |
| 147 | 147 | 25724/15 | 246122g | 28 | 1 | 2 | 1 | 1 | | 2 | 2 | 36 | 2 | 2 | 2 | 7.1 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 3 |
| 148 | 148 | 25310/15 | 241494g | 68 | 1 | 1 | | | 1 | 2 | 26 | 2 | 2 | 2 | 12.2 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 4 |
| 149 | 149 | 44647/15 | 980566f | 50 | 2 | 2 | 2 | 1 | | 2 | 2 | 12 | 2 | 2 | 2 | 11.2 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 1 | 10 | 2 | 2 | 2 | 2 | 1 | 5 |
| 150 | 150 | 41613/15 | 334123g | 45 | 1 | 2 | 1 | 2 | 2 | 1 | 2 | 14 | 2 | 2 | 2 | 5.4 | 1 | 2 | 2 | 2 | 3 | 3 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 151 | 151 | 49007/15 | 372178g | 56 | 2 | 2 | 1 | 2 | | 2 | 2 | 24 | 2 | 2 | 2 | 14 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 4 |
| 152 | 152 | 14867/15 | 182055g | 62 | 1 | 2 | 1 | 2 | 2 | 2 | 2 | 28 | 1 | 2 | 2 | 4.5 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 153 | 153 | 18945/15 | 196466g | 57 | 1 | 1 | | | 3 | 1 | 2 | 36 | 1 | 2 | 2 | 5.5 | 1 | 2 | 2 | 2 | 3 | 3 | 1 | 2 | 2 | | 2 | 1 | 2 | 2 | | 5 |
| 154 | 154 | 154 | 170705g | 51 | 1 | 2 | 1 | 2 | | 2 | 2 | 13 | 2 | 2 | 2 | 5.8 | 1 | 2 | 1 | | 2 | 2 | 1 | 1 | 1 | 10 | 1 | 2 | 2 | 2 | | 5 |
| 155 | 155 | 1274/15 | 129807g | 55 | 1 | 2 | 2 | 1 | 1 | 1 | 2 | 13 | 2 | 2 | 2 | 7 | 1 | 2 | 1 | | 1 | 1 | 2 | 2 | 1 | 10 | 2 | 2 | 2 | 2 | | 4 |
| 156 | 156 | 29790/15 | 183480g | 38 | 1 | 2 | 2 | 1 | | 1 | 2 | 36 | 1 | 2 | 2 | 9.5 | 1 | 1 | 1 | | 2 | 1 | 2 | 2 | 1 | 40 | 2 | 2 | 2 | 2 | 2 | 6 |
| 157 | 158 | 21690/15 | 218139g | 52 | 1 | 2 | 2 | 1 | | 1 | 2 | 24 | 1 | 2 | 2 | 9.5 | 1 | 2 | 1 | | 4 | 4 | 1 | 1 | 1 | 50 | 2 | 2 | 2 | 2 | 2 | 6 |
| 158 | 159 | 7647/15 | 475402f | 63 | 1 | 2 | 1 | 1 | | 2 | 2 | 40 | 1 | 2 | 2 | 8 | 1 | 2 | 1 | | 3 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 3 |
| 159 | 160 | 46071/15 | 335696G | 74 | 1 | 2 | 1 | 2 | 2 | 1 | 2 | 12 | 2 | 2 | 2 | 9 | 1 | 2 | 1 | | 4 | 4 | 2 | 2 | 1 | 40 | 2 | 2 | 2 | 2 | | 3 |
| 160 | 161 | 19557/15 | 207880G | 56 | 1 | 2 | 1 | 2 | 2 | 1 | 2 | 12 | 2 | 2 | 2 | 6 | 1 | 2 | 1 | | 3 | 2 | 2 | 2 | 1 | 50 | 2 | 2 | 2 | 2 | | 2 |
| 161 | 162 | 22672/15 | 175002G | 26 | 1 | 2 | 2 | 1 | | 1 | 2 | 12 | 2 | 2 | 1 | 3 | 1 | 2 | 1 | | 2 | 2 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 162 | 163 | 20721/15 | 217386G | 58 | 1 | 2 | 1 | 2 | 3 | 1 | 2 | 12 | 2 | 2 | 2 | 5 | 1 | 2 | 2 | 1 | 2 | 3 | 2 | 2 | 1 | 30 | 2 | 2 | 2 | 2 | | 2 |
| 163 | 164 | 3242/14 | 859495 | 77 | 1 | 1 | | | 3 | 1 | 2 | 48 | 2 | 2 | 2 | 9.5 | 1 | 2 | 1 | | 4 | 4 | 2 | 2 | 1 | 30 | 2 | 1 | 1 | 2 | | 5 |
| 164 | 165 | 7402/15 | 143760G | 55 | 2 | 2 | 2 | 1 | | 2 | 2 | 36 | 1 | 2 | 2 | 6.5 | 1 | 2 | 1 | | 4 | 4 | 1 | 1 | 1 | 30 | 2 | 1 | 2 | 1 | 1 | 5 |
| 165 | 166 | 6033/15 | 145288G | 43 | 2 | 2 | 2 | 1 | 2 | 1 | 2 | 12 | 2 | 2 | 1 | 4.5 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 166 | 167 | 9134/15 | 158563G | 50 | 1 | 1 | | | 2 | 1 | 2 | 12 | 2 | 2 | 1 | 5 | 1 | 2 | 1 | | 3 | 3 | 2 | 2 | 1 | 30 | 2 | 2 | 2 | 2 | | 2 |
| 167 | 168 | 13612/14 | 830098F | 56 | 1 | 2 | 1 | 2 | 1 | 2 | 2 | 12 | 2 | 2 | 2 | 13 | 1 | 1 | 1 | | 4 | 4 | 2 | 2 | 1 | 40 | 2 | 1 | 2 | 2 | 1 | 8 |
| 168 | 169 | 503/15 | 110515G | 67 | 1 | 1 | | | 1 | 2 | 12 | 2 | 2 | 1 | 3.5 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 169 | 170 | 12288/15 | 180578G | 57 | 1 | 2 | 1 | 2 | 2 | 2 | 2 | 12 | 2 | 2 | 2 | 5.5 | 1 | 2 | 1 | | 3 | 2 | 2 | 2 | 1 | 40 | 2 | 2 | 2 | 2 | 1 | 5 |
| 170 | 171 | 12965/14 | 183448G | 33 | 1 | 2 | 1 | 2 | | 2 | 2 | 24 | 2 | 2 | 2 | 7 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 171 | 172 | 6744/15 | 061293G | 34 | 1 | 2 | 1 | 2 | | 1 | 2 | 12 | 2 | 2 | 2 | 4 | 1 | 2 | 1 | | 2 | 3 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |
| 172 | 173 | 2935/15 | 038967G | 27 | 1 | 1 | | | 1 | 1 | 24 | 2 | 2 | 1 | 2.2 | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 2 | 2 | 2 | 2 | | 1 |